Public Health

No. 12

Main theme: **Use of Impregnated Bednets for Malaria Control**

Bayer

Hurrying home after collecting wood: The women pictured on the front and back covers of this edition represent all people living with the threat of malaria the world over. This scene was photographed in an outlying area of the Malian desert zone. This West African country, with its tropical climate and expansive swamplands along the Niger, is not constantly at risk due to malaria epidemics alone.

Public Health

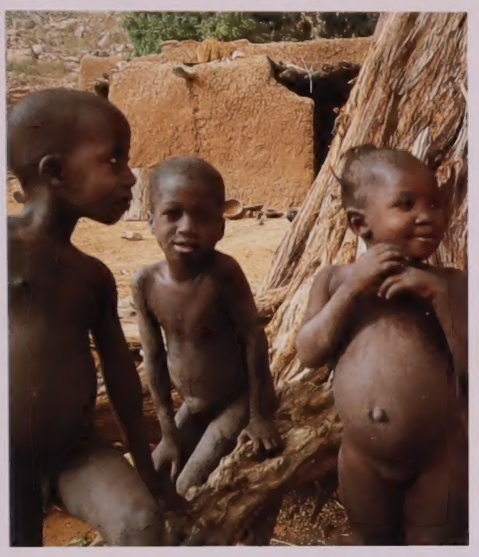
In this issue

No. 12

Four reports give an account of findings from impregnated mosquito net use in combating the malaria vector *Anopheles*. Field trials in India are in the spotlight starting on page 8, test programs in China and elsewhere are discussed starting on page 24, and the contribution starting on page 18 looks at findings from Iran.

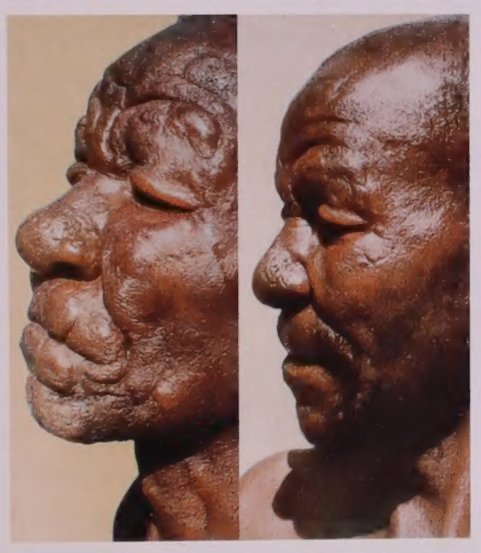
Safety aspects of pyrethroid-impregnated nets have been thoroughly tested in laboratory studies. A report of the findings can be found on pages 30-35.

The urgent necessity of increasing available funds and distributing them in an optimum manner (at municipality level and nationwide) to fight epidemics and disease is underscored in the report on page 36.



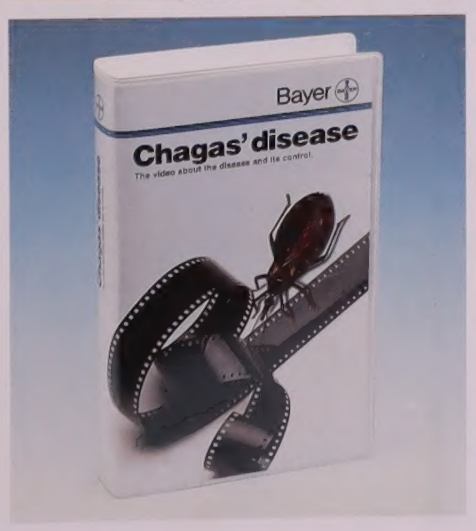
Constructive proposals for improving bilharziasis control in Africa are put forward in the report on pages 46-55.

WHO is working toward its goal of eliminating leprosy (tubercular/multibacterial) by the year 2000. MDT (Multiple Drug Therapy) is one method used to reach this goal. Information on this treatment can be found on pages 56-61.



Vector control measures raise the question of whether greater efficiency is possible through centrally managed programs or stronger reliance on local resources. For the answers, look on pages 62-68.

Important information on Chagas' disease and practical tips for planning and executing vector control programs are the subject of a new video from Bayer. For more information, turn to page 69.



For information on Bayer's commitment to tendering projects as a way of fighting epidemics and disease-carrying insects (vectors), plus structural changes made in-house to optimize the process at both national and international level, see pages 70-72.

B. Krüger
Bayer AG
Director of the Business Group
Animal Health

The publication of this, the 12th edition in our yearly series Public Health, represents a desire on the part of Bayer to renew our contribution toward intensifying communication between all those organizations which see vector control as a common, urgent concern in their work toward world health and securing good global nutrition.

Positive feedback to the articles published in Public Health attests to our endeavor to create an effective flow of information and a constructive exchange of opinion on this range of topics.

This edition emphasizes that acceptance; most of the contributions were written by authors who are scientists and experts with strong links to the World Health Organization (WHO).

It makes a topical continuation of the work which began with the previous issue of Public Health (also put together in collaboration with WHO offices), namely, depicting the conditions, situations and status quo from an objective point of view provided by the perspectives of expert observers.

The problematic nature of infestations and epidemics such as malaria, filaria, yellow fever, sleeping sickness, plague, typhoid and other major health problems facing humanity thus clearly demands the coordinated and constructive interaction of all those who can play an active part in controlling disease vectors.

Joint action is called for on the part of international organizations and national and regional institutions responsible for project management, all the way down to industry.

We at Bayer are rising to the challenge of helping to solve the problems at hand in the interest of world health. As one of the world's major internationally operative companies in this field, we offer our help in the spirit of partnership, aimed at effective cooperation. In practice (as documented in Public Health), there are many examples which corroborate our concept of seeking solutions together with partners and clients.

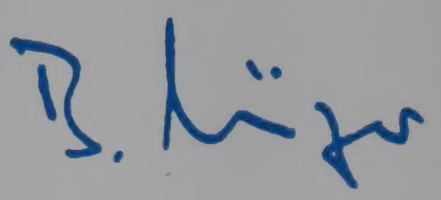
Undoubtedly a key factor in this problem-solving process are high-performance and effective products which can be applied in specific situations. In this high-cost field, we are engaged in substantial research activity geared to optimization, further developments and new discoveries. We are also addressing the complexity of the problems by initiating selected licensing and cooperation between manufacturers.

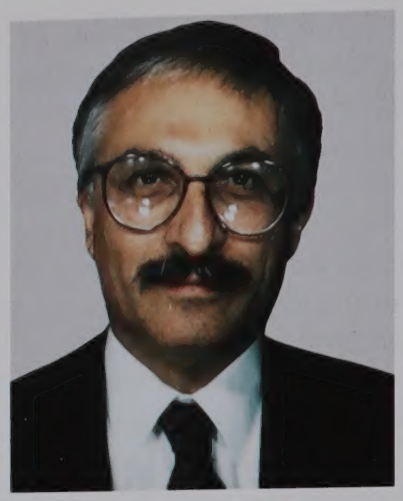
As partner to public authorities sponsoring projects and the organizations actively involved in them, we are making every effort to be of assistance through such value added services as supplying preparatory information, training in the field and diverse service programs.

In response to the increasing complexity of tasks that lay ahead, vector control measures are developing into ever more comprehensive, multi-faceted projects. We at Bayer are prepared to extend our commitment to finding good solutions into the future.

I would like to take this opportunity to express a word of thanks to each and every person who shares in this dialogue - be it through written comments on specific articles in Public Health or through direct contact with one of the authors.

Very special thanks go out, of course, to the authors themselves, whose expert and authoritative contributions help shape the reputation of a publication such as Public Health.





Dr. K. Behbehani
Director of the Division of Control of Tropical Diseases of the World Health Organization (WHO)

One of the important themes of this issue of Public Health magazine - " Malaria Risk " - brings to the fore a subject whose importance will increase steadily in the years and even decades to come.

Among the diseases that afflict the tropical regions of our planet, malaria exerts the heaviest toll in terms of death and suffering. Between 300 and 500 million individuals are infected, of whom more than 20 million will die over the next ten years unless we find new, or improve existing, methods for controlling this disease. More than 40% of the total world population is at risk.

The World Health Organization (WHO) knows only too well the hardiness of both the anopheles mosquito and the different forms of malaria parasite, of which *Plasmodium falciparum* is the most feared. Efforts in the 1950's and 1960's to eradicate malaria failed in several countries for a variety of reasons, not least of which was the development of mosquito resistance to insecticides and of parasite resistance to anti-malaria drugs.

Today we are making some gains against the disease and the vector, but progress is painfully slow. We are very hopeful of being able to develop a viable, one-shot malaria vaccine for mass administration. But whatever means are at hand must be deployed at once on an ever wider scale if - as many scientists believe - "global warming" proves to be a reality. Already there are signs that malaria is "drifting" appreciably north and south away from the tropics.

Among the existing weapons in our armory is a technique which blends chemical methods for killing insect vectors and physical methods to prevent human contact with the insects. The principle of using curtains and bednets in malarial areas dates back to antiquity. The earliest recorded use of bednets was in the 6th century B.C. in the Middle East; 500 years later, Queen Cleopatra of Egypt used "a handsome bednet made of cloth of gold." The Venetian traveller Marco Polo noted in the 13th century A.D. that people of high rank protected themselves at night with bednets.

As mainly nocturnal blood-feeders, anopheles seek their sustenance wherever people sleep. As a physical barrier only, bednets have three main disadvantages: if they are torn or not well tucked under the mattress, mosquitos can make an entry; if sleepers come in contact with the net, the insects bite them through the mesh; and mosquitos remain alive within the sleeping quarters. Recent surveys demonstrated that, under field conditions, untreated bednets do not reduce malaria transmission sufficiently to decrease morbidity.

The obvious answer is to combine the physical barrier with a repellent or, better still, an insecticide, a concept widely developed and used before and during the Second World War. But repellents are short-lasting and not wash-resistant, and the mosquitos continue to threaten the family and community.

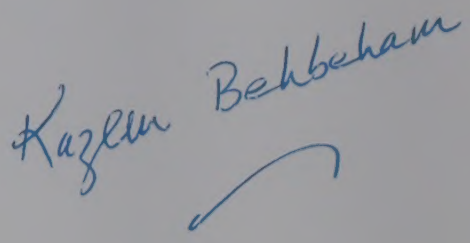
Classical insecticides tested in the past (even DDT) did not produce satisfactory results, but the availability of pyrethroid opened new possibilities. The first field trials at village level of bednets impregnated with pyrethroid (permethrin) were made in 1984 at a WHO Collaborating Center in Burkina Faso. Anopheles were not only deterred from entering homes that were so equipped, but also a certain percentage were killed and blood-feeding on humans was prevented to an appreciable degree. Trials on a much larger scale followed in Africa, South America, Southeast Asia and the Western Pacific.

Today large-scale use of pyrethroid-impregnated mosquito nets (and other materials) has successfully reduced malaria transmission by more than 90% in several communities in Burkina Faso, Cameroon, Congo, Gambia, Tanzania and Zaire. They have also helped reduce the incidence of malaria in Vietnam and brought spectacular results in areas of China. The nets are proving effective against other tropical disease vectors such as sandflies, bedbugs, fleas and lice.

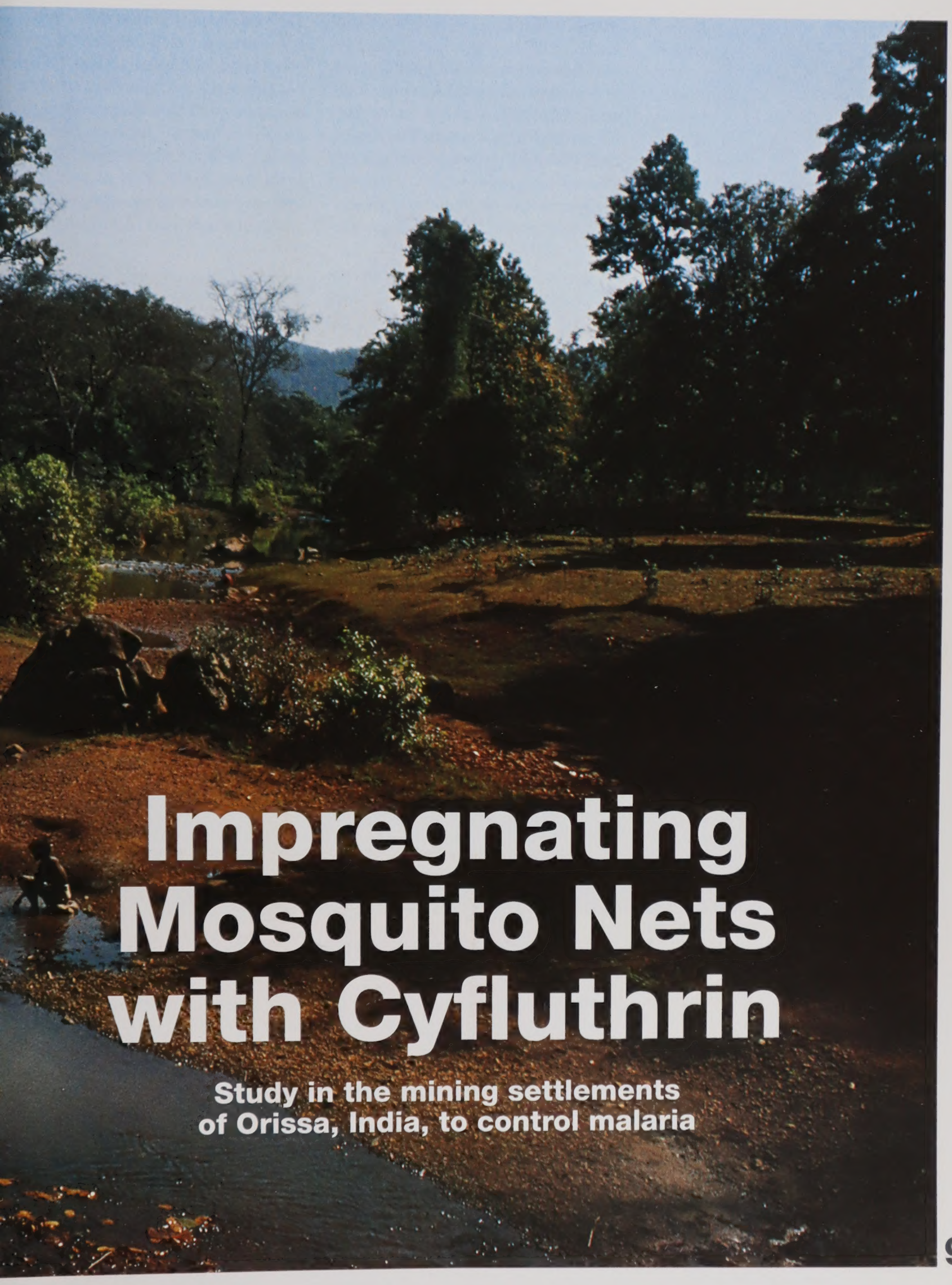
Local communities, usually under the supervision of a community health worker, can readily undertake the task of dipping the nets in solution, and thus actively participate in protecting their own welfare. A cost comparison in China has shown that deltamethrin treatment of people's own nets costs only one quarter of the price of spraying the same houses with DDT.

If climate change is going to mean the advance of mosquitos and other disease vectors into areas outside the tropics, there is no time to lose. While research must continue into vaccines and other promising methods of control, barrier methods between humans and vectors such as impregnated curtains and bednets must be deployed, made permanently accessible to everyone and further improved so that the sorry cycle of disease transmission, which already causes sickness and death over so much of the globe, can be interrupted.

In order to forestall resistance problems in the future, operational research into the formulations and concentrations of existing insecticides, and the development of new insecticides, will be essential. WHO is confident that its long-standing amicable collaboration with the pharmaceutical industry will continue to bear fruit in this field, and that new and ever more effective solutions will be found for a public health problem that has such heavy consequences for vast numbers of our fellow mortals.



Dr. K. Behbehani, Director of the Division of Control of Tropical Diseases, WHO, has written this introduction in a private capacity. The views expressed do not imply the endorsement of any commercial company and/or product, either by the author or by the World Health Organization.



Impregnating Mosquito Nets with Cyfluthrin

Study in the mining settlements of Orissa, India, to control malaria

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Introduction

About two million malaria cases are reported in India every year, and 38%-40% of these cases are *Plasmodium falciparum*. Rural malaria control is based on the indoor residual spraying of DDT, HCH and malathion supported by case detection and treatment. Malaria is the most prevalent disease in Orissa State of India, which accounts for one-seventh of the total malaria cases, 31.7% of all *P. falciparum* cases and 34.2% of all malaria deaths in India (Table 1). DDT is sprayed to control malaria in the state. Orissa has a vast stretch of forested hills inhabited by the tribal population and endowed with minerals such as iron ore, bauxite, graphite, quartz, lime stone, etc. Malaria is the most prevalent disease in the tribal settlements and *P. falciparum* is the predominant infection. Spraying of insecticides and other methods of malaria control have not been very effective in these areas. Over the last few decades exploitation of natural resources particularly in the forested hills has resulted

Table 1: Malaria in Orissa State vis-a-vis India (1993)

Parameters	India	Orissa State	% in Orissa
Population (million)	833.9	31.2	3.7
Malaria cases (million)	2.2	0.32	14.5
P. falcip. cases (million)	0.69	0.27	31.7
Deaths due to malaria	345	118	34.2

Pages 8 and 9
Streams are major breeding habitats of *An. fluviatilis*.
Mining settlements are located near the streams.

in further spread of malaria and exposure of non-immune immigrants to falciparum malaria (Yadav, 1991).

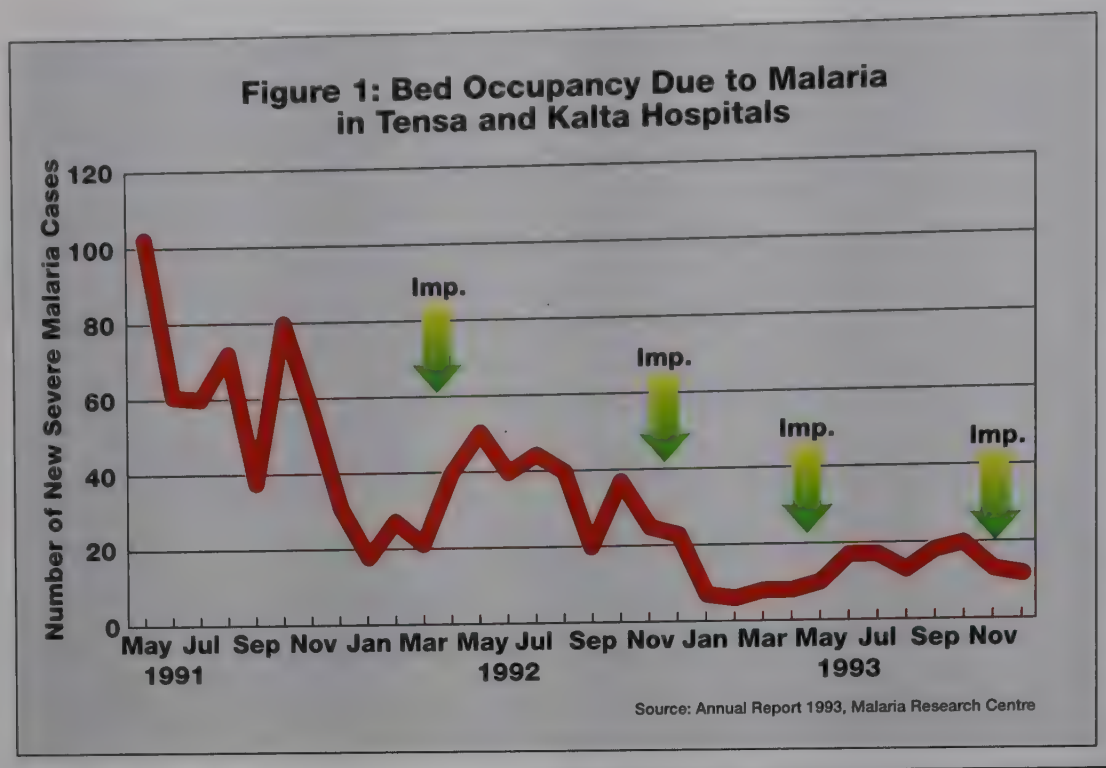
Malaria incidence

Epidemiological investigations from 1989 to 1991 in northwest Orissa revealed high malaria transmission. The number of new malaria cases per 1,000 population per year ranged from 127-481, proportion of malaria in all febrile cases ranged from 37%-52% and spleen rate in children aged two to nine years ranged from 17%-100%. *P. falciparum* accounted for 77% morbidity, *P. vivax* 19%, *P. malariae* 1% and mixed infections 3% (Yadav et al., 1990). In another study in forested settlements of two major iron ore mines in northwest Orissa, malaria was the main public health problem. In this population parasite rate was 14%-24%, slide positivity rate was 35%, spleen rate was 37%, bed occupancy due to malaria in mining hospitals ranged from 47%-62% and loss to individuals due to malaria averaged Rs. 142 or US$8.3 per capita (1989 prices) per malaria episode (Yadav et al., 1991). Residual spraying of DDT to interrupt transmission was unsuccessful and people of low socio-economic status suffered immensely.

Mosquito net strategy

Major obstacles in malaria control *inter alia* are chloroquine resistance in *P. falciparum*, vector resistance to DDT, poor spray coverage, frequent mud-plastering of sprayed walls, poor housing, living style resulting in excessive man-mosquito contact, operational problems and poor health infrastructure. As a result, malaria control in these areas requires the application of new methods, and one such possibility was the use of mosquito nets. Mosquito net technology is not new: during World War II a poster encouraging the use of mosquito nets to protect from malaria appealed: "Do not go to bed with a malaria mosquito! Sleep under a net! Keep it repaired! Tuck it in! Be sure no mosquito is inside waiting for you! Fight the peril behind the lines!"

Barsuan iron ore mine in the forest hills.

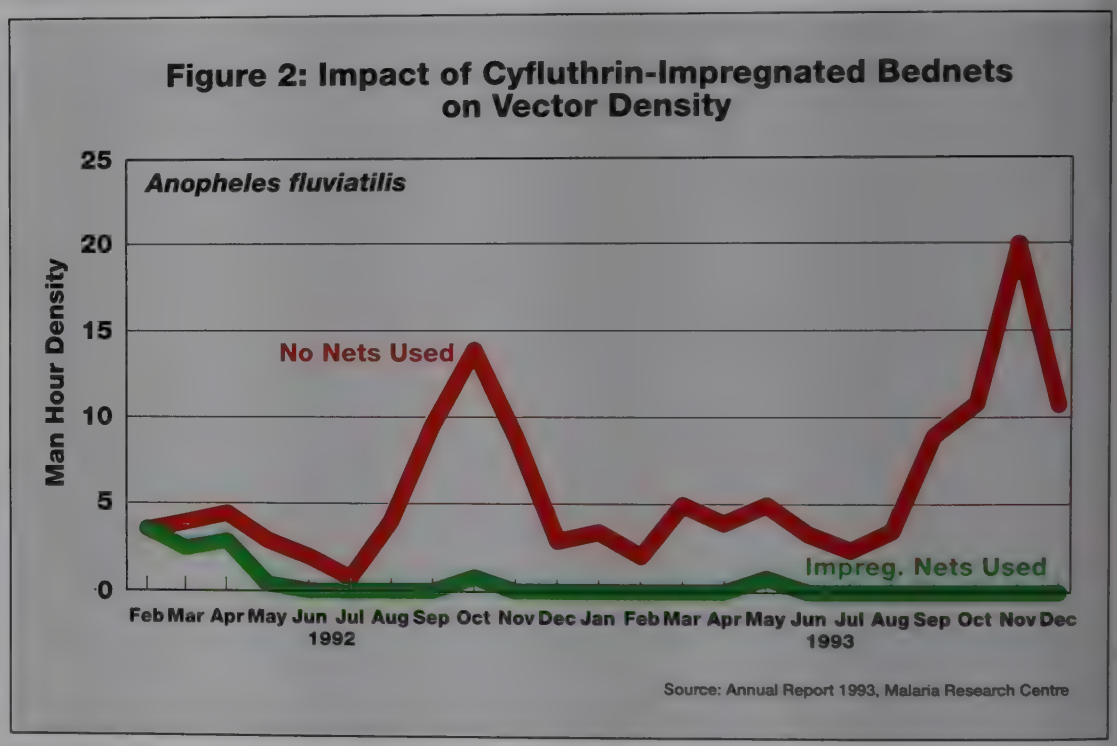


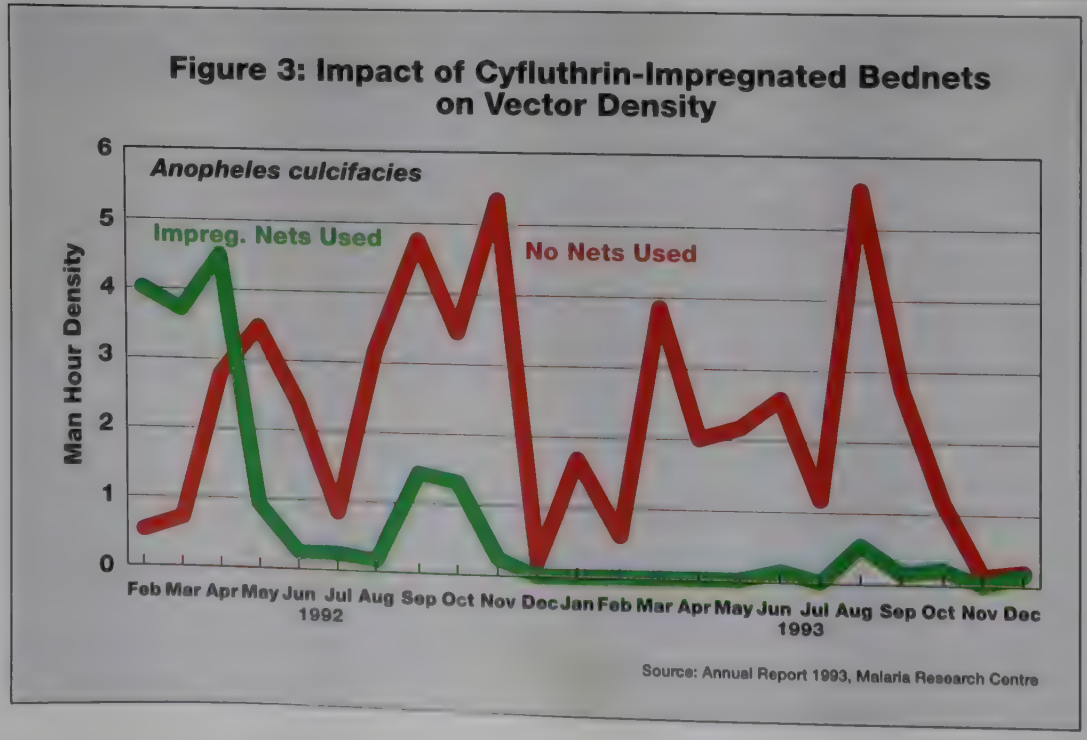
in malaria control (Rozendaal and Curtis, 1989). In this article we report the results of cyfluthrin (Solfac EW 050)-impregnated mosquito nets in malaria control at mining settlements in Orissa, India.

Trials among the mining population

The Barsuan, Tensa and Kalta iron ore mines (population 11,726), operating under the Steel Authority of India Limited (SAIL), were selected for the cyfluthrin-treated mosquito net trials. Three settlements in the same area, Toda, Khandadhar and Sashkela (population 2,920), were chosen as control sites without mosquito nets. The study and control settlements were located in deep forest at an altitude of 700-800 m, with tropical climate and high rainfall (average 1,350 mm). People live in huts with tiled roofs or in brick-built houses. Major occupations were opencast mining and collection of forest products, with some households dependent on agriculture. The ratio of humans to cattle ranged from 23:1 to 27:1 in different settlements, thus providing enhanced man-mosquito contact. SAIL hospitals at Kalta and Tensa mines provide free treatment to the mining population. Prior to the introduction of impregnated mos-

Impregnation of mosquito nets with an insecticide which has rapid knockdown action is more effective in preventing man-mosquito contact than untreated nets. This development in mosquito nets has emerged as an important advance in the control of malaria. Synthetic pyrethroid insecticides are preferred for impregnation. These insecticides have the property of fast knockdown action on insects and are safe to warm-blooded animals due to poor dermal absorption. Use of impregnated mosquito nets against a number of vector species in endemic countries has produced highly encouraging results





quito nets there was 47%-62% hospital bed occupancy due to malaria alone. Untreated mosquito nets were largely used by the people of these settlements to ward off mosquitos (Figure 1).

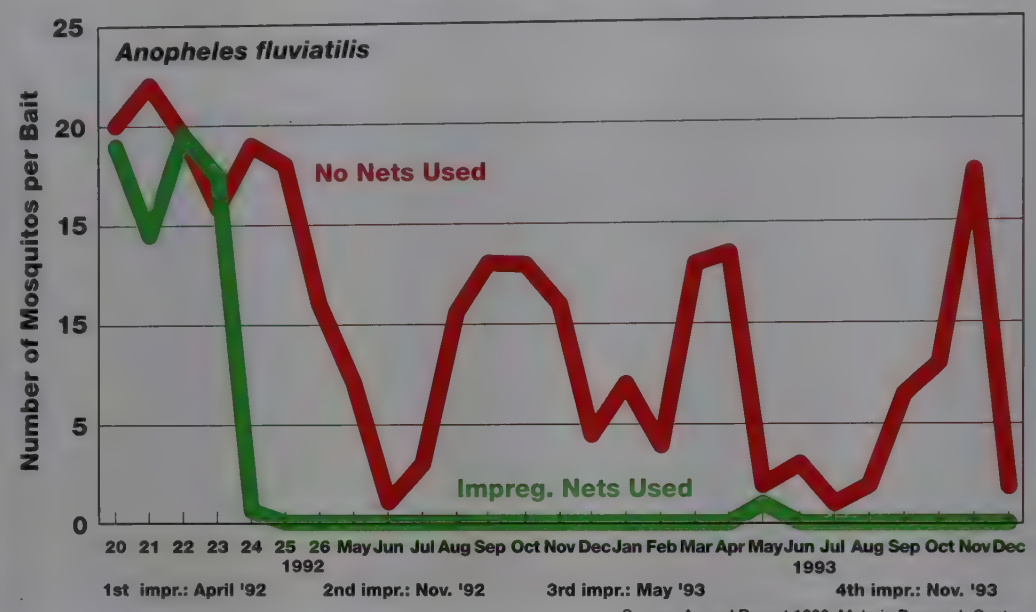
Field work was initiated in February 1992. Baseline data on demography, malaria prevalence, vector breeding habitats, use of mosquito nets and sleeping habits were collected. In the three settlements selected for intervention, nylon nets impregnated with cyfluthrin @ 50 mg a.i./m^2 were distributed free of cost. All age groups were covered. Health education camps and demonstrations were organized in the settlements and schools on proper usage and upkeep of mosquito nets. Fortnightly active malaria surveillance was established to monitor parasitological indices. All cases of fever or a history of fever were given presumptive chloroquine treatment (10 mg/kg body weight) after taking a blood smear. Malaria cases were given radical treatment (*P. falciparum*: total of 25 mg/kg body weight chloroquine and 45 mg primaquine or 1,500 mg sulphadoxine/pyrimethamine and 45 mg primaquine: *P. vivax*: total of 10 mg/kg chloroquine + 75 mg primaquine in five divided doses; all adult doses). Children were given proportionately low dosage; infants and pregnant women were not given primaquine. Serious cases were referred to hospitals and treated intravenously with quinine. Bioassays showed that cyfluthrin was fully effective in killing *Anopheles fluviatilis* for up to 12 months on unwashed nets. However, from the seventh month onwards the efficacy on *Culex quinquefasciatus* declined. Therefore, a six-month cycle of mosquito net re-impregnation was adopted, i.e. during the two-year period mosquito nets were impregnated in May and November 1992 and May and October 1993, with a dosage of 50 mg/m^2 cyfluthrin maintained in all treatments. All mosquito net treatment was carried out by the communities under the supervision of the staff of the Malaria Research Centre.

Health education camp in the school. Demonstrations were given on causes of malaria and usage and proper upkeep of mosquito nets.

Vector density

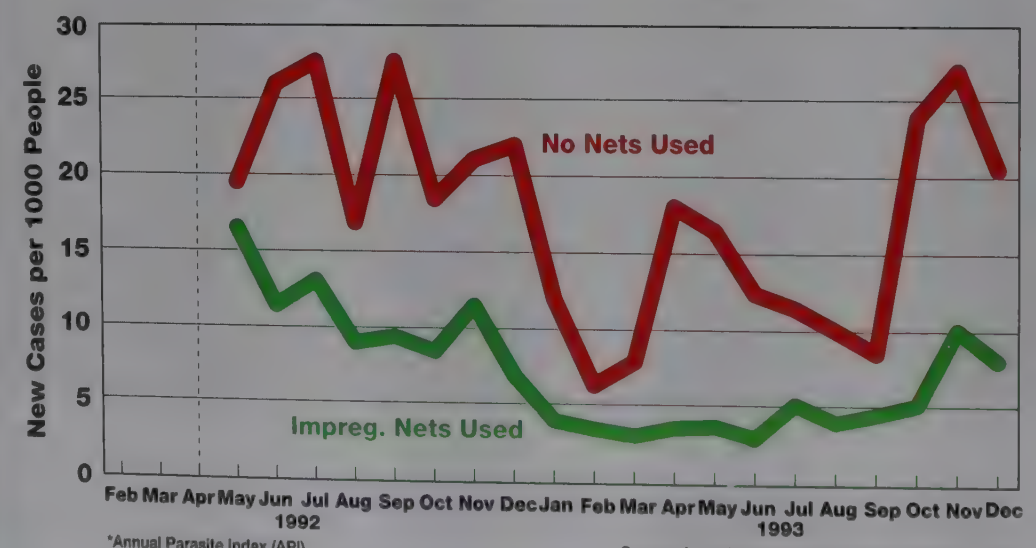
Anopheles fluviatilis was the main vector in the mining settlements. It breeds in streams, channels and seepages. *An. culicifacies* was present in low numbers and its role in transmission was questionable. It breeds in rain pools, flooded fallow fields and rainwater collections. Monitoring of *An. fluviatilis* resting populations before the introduction of mosquito nets from February to April 1992 showed that indoor man hour densities (MHD) ranged from 2.2 to 3.3 in the intervention area and 3.5 to 4.0 in the control area. After the introduction of cyfluthrin-impregnated mosquito nets in May 1992, vector density (MHD) declined sharply and remained at about zero level (0 - 0.25) for the two-year study period (Fig. 2). *Anopheles culicifacies* densities also remained very low in the intervention area compared to the control (Fig. 3). However, in the control area without mosquito nets *An. fluviatilis* and *An. culicifacies* MHD ranged from 0.8 to 19.9 and 0 to 6.5, respectively. Thus, the introduction of cyfluthrin-impregnated mosquito nets resulted in a sharp fall in the densities of *An. fluviatilis* and *An. culicifacies*.

Figure 4: Impact of Cyfluthrin-Impregnated Mosquito Nets on Biting Activities



Source: Annual Report 1993, Malaria Research Centre

Figure 5: Reduction of Malaria using Cyfluthrin-Impregnated Bednets*



*Annual Parasite Index (API)

Source: Annual Report 1993, Malaria Research Centre

Vector biting

Prior to the introduction of treated nets, night catches of *An. fluviatilis* on human baits showed that more than 96% of bites took place between 9 pm and 4 am with a peak at midnight, and the man-biting index (proportion fed on human blood) was >95%. Since most people were inside the mosquito nets during biting hours of *An. fluviatilis* it was obvious that impregnated mosquito nets prevented vector biting (Fig. 4). Before the trial started, the mean number of mosquito bites in the treated mosquito net area was 14.5 to 19.5 bites/man/night, and in the control area 16 to 22 bites/man/night. After the introduction of treated mosquito nets, vector biting on baits inside partially lifted nets was reduced to zero (except 0.12 in June 1992 and 0.5 in May 1993). In the control area biting fluctuated from 0.75 to 19 bites/man/night for the two-year period. The biting rate of *An. culicifacies* was very low in both the areas, so the data have been ignored. It was observed that mosquito biting was prevented for sleepers inside the treat-ed mosquito nets even though the nets were damaged, had holes or were not properly tucked, leaving space for mosquito entry. Thus cyfluthrin-treated mosquito nets almost completely prevented man-mosquito contact.

Malaria incidence

Reduction in vector density and man-biting rate resulted in a major reduction in malaria cases among the users of treated mosquito nets. During the first year malaria API (no. of malaria cases/1,000 population/year) in the intervention areas was 100, compared to 223 in the control, which means a 57% drop in incidence compared with the control during the first year. During the second year API in the mosquito net areas was 58 com-

pared with 175 in the control, i.e. 66.9% lower compared with control. Similarly, slide positivity rates in the first and second years were 32.3% and 25.3% in the intervention area and 37.8% and 51.7% in the control area, respectively. Thus the intervention area showed a reduction of 14.6% in the first year and 51% in the second year compared with the control area. In the second year annual slide falciparum rate also decreased by 35.6% in the intervention area compared with control. Thus there was marked reduction of malaria, and the use of cyfluthrin-impregnated mosquito nets prevented generation of new cases of malaria among the mining community.

Hospital bed occupancy

In the two mining hospitals 600 to 1,000 serious malaria cases were admitted for treatment each year. In the year preceding the start of the mosquito net study, i.e. May 1991 to April 1992, 656 malaria patients were admitted for treatment from the intervention areas. Hospital admissions for malaria declined to 328 in the first year of the trial and further to 170 in the second year (Fig. 6). Total hospital admissions also dropped from 2,388 to 1,907 in the first year and further to 1,388 in the second intervention year. Since malaria transmission, and thus also hospital admissions, remained at about the same level in all other mining settlements, we conclude that reduction in hospital admissions was due to the introduction of cyfluthrin-treated mosquito nets.

Social acceptability

Sociological surveys revealed that the average usage of impregnated mosquito nets was >74%. The impregnated mosquito net program was widely appreciated by the mining population as it nearly eliminated mosquito bites, nuisance insects, head lice and provided relief from fever and malaria, etc. Human toxicity evaluation has been done and prelimi-

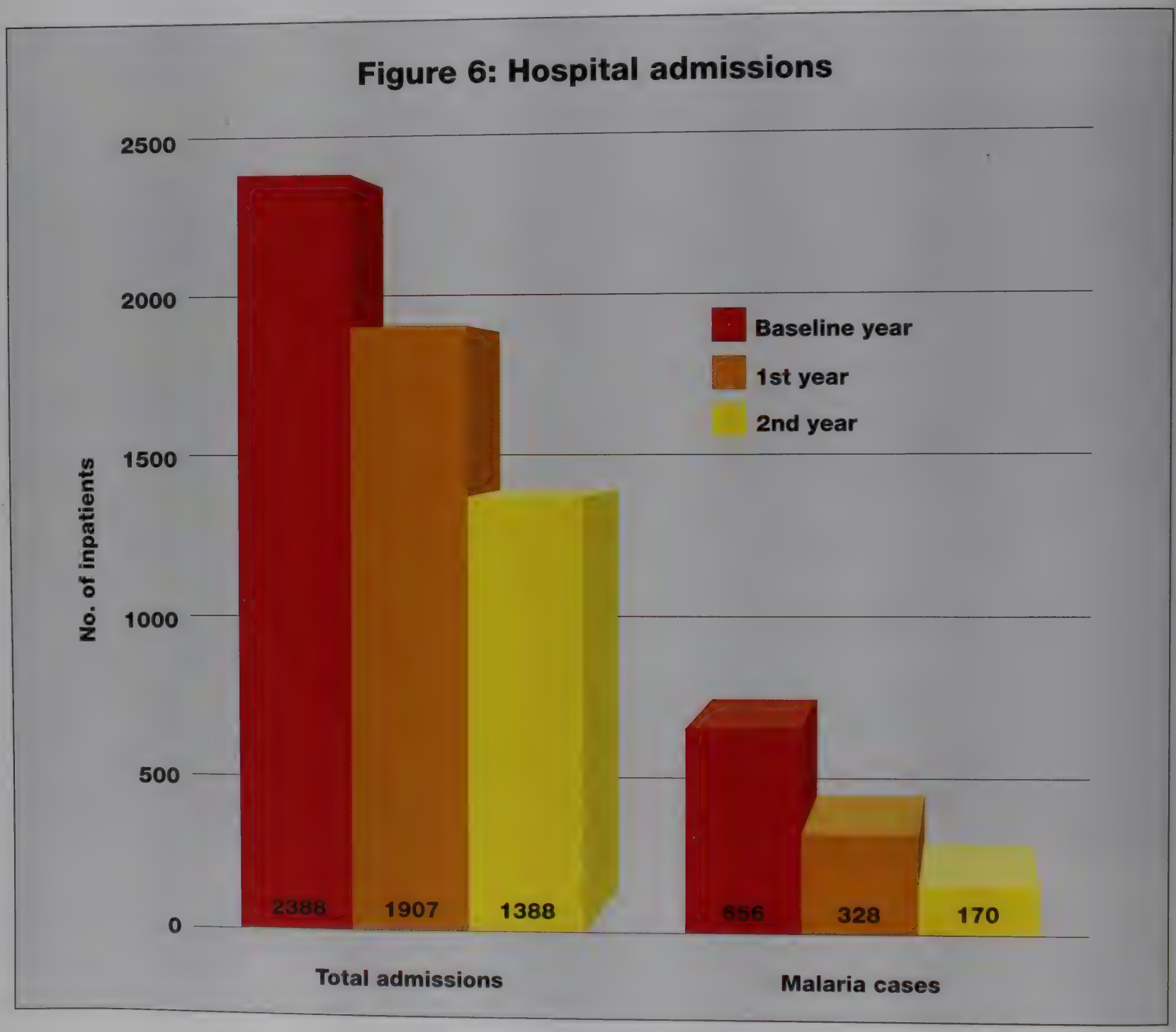
Communities impregnating mosquito nets under the guidance of a project staff.

liminary analysis of data related to clinical examination and biochemical, nerve conduction and lung function testing indicate good safety of cyfluthrin on users and impregnators of mosquito nets. Users of treated mosquito nets and those involved in impregnation did not complain of any adverse reaction. People were very enthusiastic in their acceptance of the mosquito nets, ensuring proper use and maintenance. They washed and mended nets and participated in impregnation, drying and related work. Several industrial outfits in the region have shown interest in the use of impregnated mosquito nets as a means of preventing malaria and warding off mosquitos. Prior to the introduction of impregnated mosquito nets, placement of service personnel and industrial security staff in the mining settlements was considered a disadvantage, and within two years this perception had completely changed to a positive one. The cyfluthrin-impregnated mosquito net program in Orissa has thus brought new hope of freedom from malaria.

Acknowledgements

Thanks are due to Bayer AG, Germany, for gratis supply of Solfac EW 050 and to our colleagues Dr. T. Adak and Mr. M.A. Haque for their participation in completion of the trial.

Figure 6: Hospital admissions



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A Village-scale Trial of OMS 2012 Cyfluthrin (Solfac WP 10) for Control of Malaria Vectors in Southern Iran (1992 - 1993)

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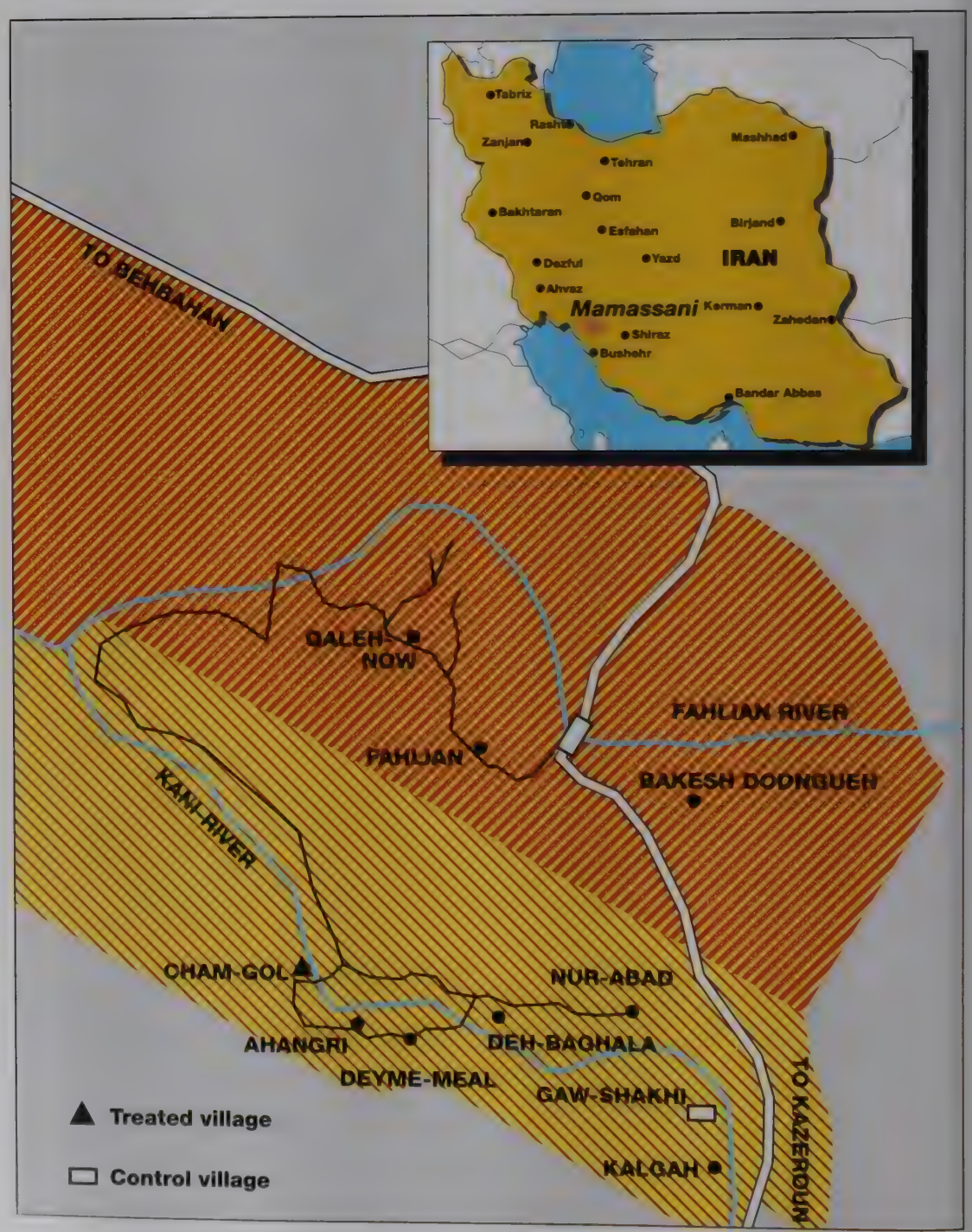
School of Public Health
Institute of Public Health Research

Introduction

Following the emergence of malaria vector resistance to DDT (1957), dieldrin (1960) and Malathion (1970), the introduction of Propoxur in Southern Iran in 1977 and the continuing search for improved methods of vector control made it necessary to examine alternative safe insecticides with improved residual effects for future use. For this reason the effectiveness of the α-cyano pyrethroid cyfluthrin (OMS 2012) was examined in village-scale trials in Southern Iran during 1992 and 1993.

The aim of this trial in the



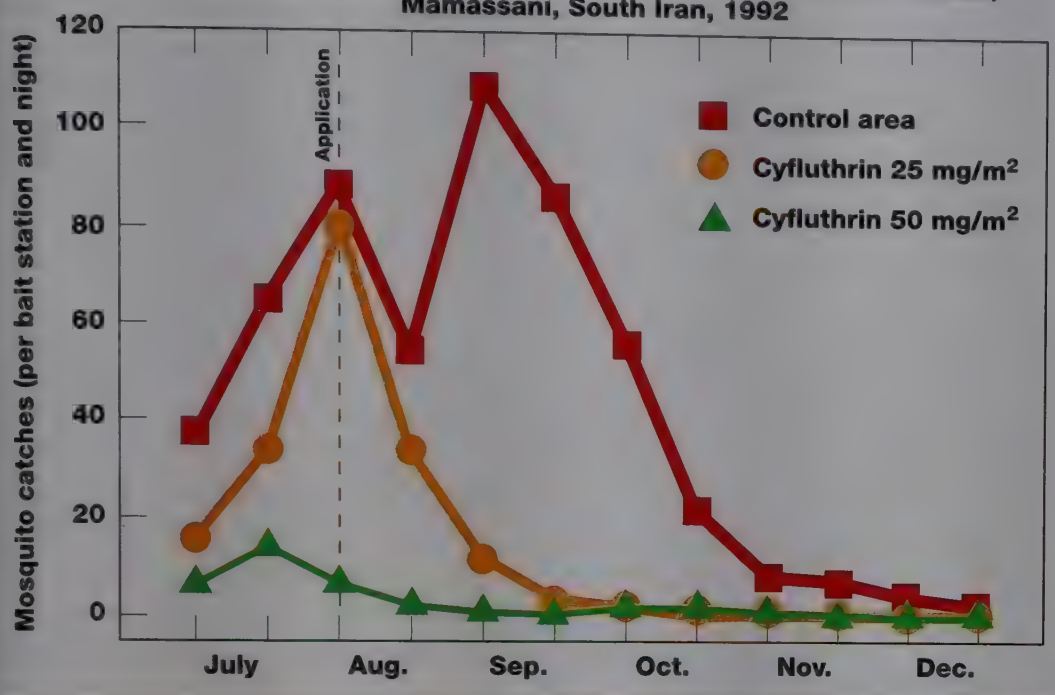
Mamassani region was to assess the insecticide's efficacy, especially its impact on malaria vectors, its safety to spraymen and the residential population and acceptability by village inhabitants.

city and 8002 nozzle. The formulation mixed freely without clogging or other difficulties.

The safety evaluation was based on health monitoring which had villagers name subjective symptoms from local effects of the insecticide on the skin, the respiratory tract and the eyes. Personal protective measures taken by the spraymen included wearing protective overalls, rubber gloves, head coverings and surgical masks. Safety instructions based on personal experience and the manufacturer's recommendations were followed during the procedure.

Fig. 1: Reduction of Mosquito Night Biting Activity after Application of Cyfluthrin

Catches from Animal Bait Stations in Trial and Control Areas, Mamassani, South Iran, 1992



Material and methods

The area selected for the evaluation of cyfluthrin is a mountain-ringed plateau at an altitude of 750 m with a temperate climate and relative humidity up to 70%. The main breeding sites for the mosquitos are rice fields, irrigation canals and river banks.

Three villages at suitable distances from each other were selected for the study, one serving as control site.

Cyfluthrin as WP 10% was sprayed in the first village (Kalgah, population 456) at a rate of 25 mg a.i./m² and in the second village (Chamgol, population 661) at a rate of 50 mg a.i./m². No spraying was carried out in the control village, Bakesh Dodangeh, population 605.

The sprayer used was an X-Pert Hudson pump with a 10-liter capa-

Preparation of the spray formula with cyfluthrin WP 10

An entomological evaluation took place pre- and post-spraying in the two treated villages and at the control site. The efficacy of cyfluthrin was studied by the following methods:

a) Indoor pyrethrum spray collection (total catches) carried out at 15-day intervals at eight fixed collection stations (four human and four animal shelters);

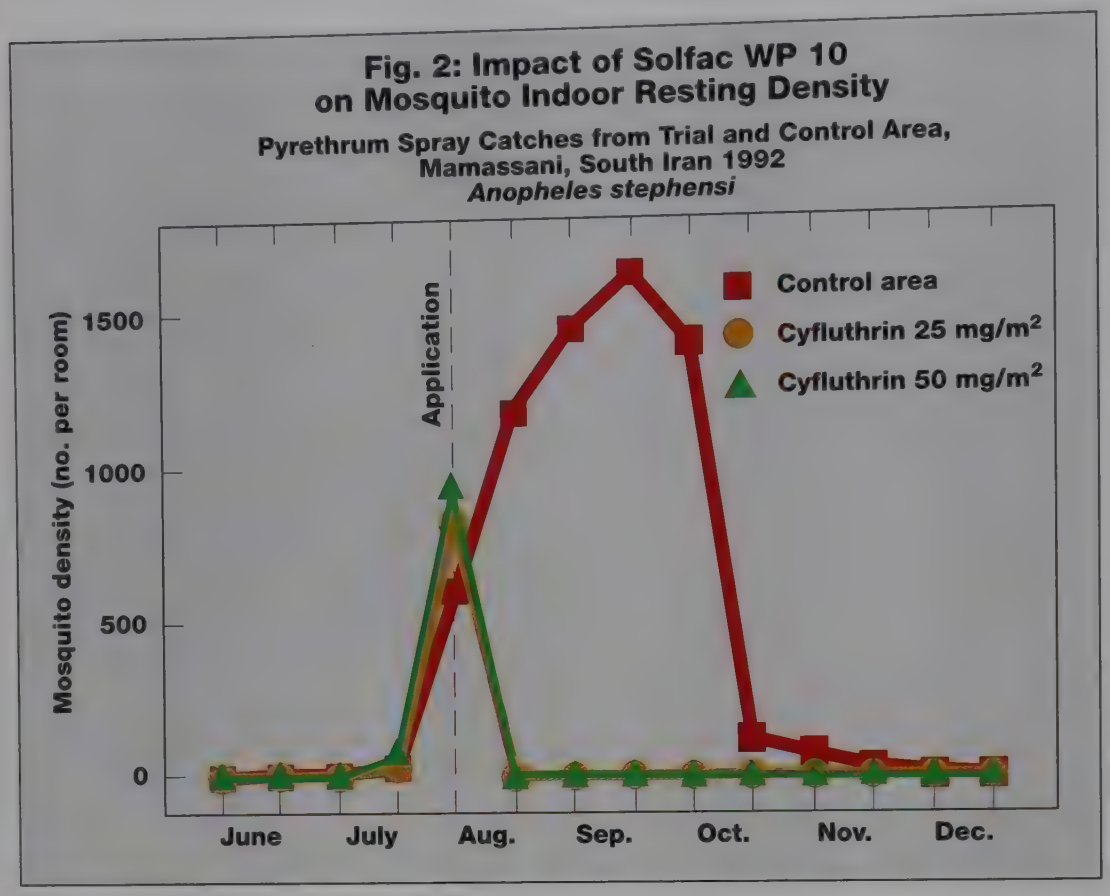
b) Bi-weekly floor sheet collections;

c) Exit window traps: observation of 24-hour mortality every 15 days;

d) Night-biting collections: full night catches on human and animal baits;

e) Four artificial pit shelters installed in each village and checked every 15 days;

ceilings of the treated rooms. Exposure time was one to five hours and the observation period lasted 24 hours.



f) Vector age determination: abdominal ages (empty, blood-fed, semi-gravid and gravid) and ovary dissections by Detionova's method.

g) Larval collection: larval density assessed by counting the number of larvae per 10 dips.

Bioassay tests were carried out on various surfaces of the interior walls and ceilings of the rooms and the animal shelters in the sprayed villages. A laboratory blood-fed strain of *Anopheles stephensi* females was used.

The exposure time was 30 minutes, after which the mosquitos were placed in fresh cages and checked for 24-hour mortality. The bioassay tests took place at 15-day intervals using the standard WHO method.

Airborne effect: four cages with 50 blood-fed *A. stephensi* were installed 40-50 cm from the walls and

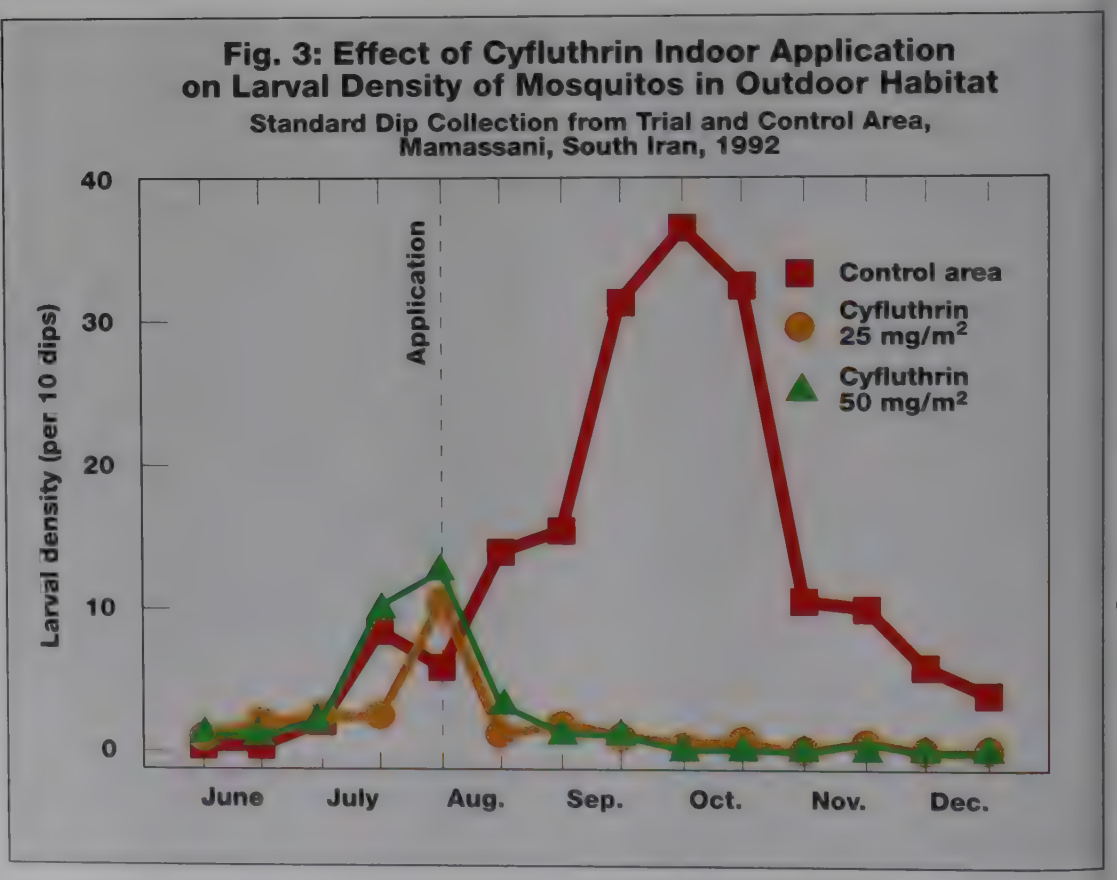
Results

● Safety

The spraying squats readily accepted treatment with Cyfluthrin Wettable Powder 10. There were no major complaints of negative impacts related to cyfluthrin, neither from the spraymen nor from the inhabitants. Only a few spraymen reported slight skin burning due to contamination with the insecticide during the procedure. All these effects could be traced to the nature of pyrethroids and were fully reversible.

● Indoor resting density

Evaluation of indoor resting density took place before and after spraying, starting in June (60 days before spraying) and continuing for 125 days post-spraying. Weather conditions during this timeframe permit activities to be carried out against the main malaria vectors (*Anopheles stephensi*, the only vectors for which results are shown here; the secondary vectors are *A. d'thali*, *A. superpictus*, *A. fluviatilis* and *A. saccharovi*.). In the village sprayed with 25 mg cyflu-



thrin/m², maximum density per room was 10 one day prior to spraying. After five days the density of all anopheline species had dropped to zero and remained there for the next 20 days, when it increased to a maximum of 2.3 per room.

In the village treated with 50 mg cyfluthrin/m², the density of *A. stephensi* was 922.1 one day before spraying. By the fifth day post-spraying it had decreased to zero, where it remained for up to 30 days. At a maximum of 0.62 anophelines per room, total density was still low 122 days after spraying. In the control village total density had increased to 1,882 per room by September, 1,630.5 accounted for by *A. stephensi* alone.

● Blood digestive stages

In the sprayed villages most of the collected anophelines were semi-gravid and gravid before spraying; after spraying all captured anophelines were empty or freshly blood-fed. In the control village the ratio of semi-gravid and gravid anophelines was high.

● Floor sheet collections

Collection started one day before spraying: no dead mosquitos were collected on the sheets. Five days after spraying, 195 dead *A. stephensi* were found in the village treated with 25 mg/m² and 211 were found in the village treated with 50 mg/m². Almost no semi-gravid or gravid anophelines were collected on floor sheets and no parous anophelines were observed.

● Exit window trap collections

In the 30 days prior to spraying, all captured anophelines remained alive throughout the 24-hour observation period. After spraying 100% mortality was observed for up to 65 days in the 25 mg/m² village, with the parous rate remaining at zero for as long as 125 days; in the village sprayed with 50 mg a.i./m², both these effects could be observed until the end of the study. In the control village no mortality was observed in the exit window traps even after 24 hours of observation.

● Night-biting collections

The density of *A. stephensi* prior to spraying was 25.5 per human bait, which steadily decreased to zero over the 123 days following the spraying period. This reflects the endophilic conditions of this primary vector species. The same pattern could be observed in the village treated with 50 mg/m².

Indoor application with a knapsack sprayer

● Larval collection

In contrast to the untreated village, the two treated villages showed a decrease in larval density per 10 dips. At the end of the observation periods larval density in the treated villages was lower than in the period before spraying, whereas in the untreated village the larval density was much higher than at the outset.

● Biological evaluation

The results of the bioassay test at the rate of 50 mg showed a mortality rate of 100% on mud plaster, lime-washed surfaces, cement and wood surfaces up to 35 days after spraying. Ninety-five days post-spraying the mortality rates on these surfaces were 90%, 85%, 65% and 98%, respectively. Mortality had decreased to 69%, 64%, 62%, 59% and 76%, respectively, 170 days after spraying.

Bioassay results from the village treated with 25 mg a.i./m^2 showed that mortality 35 days after spraying was 95% on mud, 86.6% on lime-washed surfaces, 78.6% on cement and 100% on wood surfaces. One hundred and fifty-five days post-spraying mortality on the surfaces was 52%, 36%, 35% and 56%, respectively.

Airborne efficacy: A one-hour exposure to the insecticide caused no mortality in the caged mosquitos.

● Dissection results for female mosquitos

In the untreated village the parous rates did not change significantly during the observation period. Parous rates in the treated villages showed a dramatic decrease after spraying.

Discussion

The main vector in this area of Southern Iran is *A. stephensi*, whose density peaks once a year in August/September. This species has endophilic and endophagic characteristics, with a preference for bloodmeals from animal sources. Secondary vectors are *A. fluviatilis*, *A. d'thali* and *A. superpictus*. All these have two density peaks - one in the spring and one in the autumn. These species are mainly exophilic and exophagic, with *A. d'thali* also preferring animal blood.

The total anopheline collections reflect this pattern, with *A. stephensi* the most abundant species in the indoor collections. The overall anopheline density peak takes place in September/October, but the transmission season lasts close to six months, starting as early as mid-May and lasting until mid-October. Normally, insecticide application is done in June/July before the population density is high, and one spray round per year is sufficient in the region. For the experimental reasons of the trial, however, the application was done in August, when population density is already increasing. The effects on indoor population density were dramatic compared to the undisturbed population increase in the unsprayed village (Fig. 1).

Breaking the cycle of transmission means preventing the mosquito from taking a bloodmeal. In the unsprayed village (Table 2) the three digestive stages reflecting blood-meal uptake (blood-fed, semi-gravid and gravid) accounted for 96% of the *A. stephensi* caught between July and December. These stages were reduced to zero in the 50 mg trial area and to very low percentages in the 25 mg village. For the main vector this indoor residual spraying was an effective means of reducing infectious bloodmeals. The parous rate also dropped to zero in both treated villages, implying that the overall age of the mosquito population likewise went down.

Tab. 1: Impact of Cyfluthrin Residual Spray Application on Feeding and Parity Ratio Evaluation from Pyrethrum Catches, Mamassani Area, South Iran, 1992
Anopheles stephensi

	Cyfluthrin treated 25 mg/m^2					Cyfluthrin treated 50 mg/m^2				
Month	No.:	Unfed	fed	nulli-parous	parous	No.:	Unfed	fed	nulli-parous	parous
Aug.	195	35	160	174	21	211	36	175	199	12
Sep.	31	5	26	30	1	40	25	15	33	1
Oct.	4	0	3	4	0	3	2	1	3	0
Nov.	2	0	1	2	0	5	3	2	5	0

Exit window trap collection is the method of detecting the number of mosquitos driven out of sprayed houses by interaction with the insecticide (irritancy, repellency, airborne effects, etc.). In the unsprayed village the number of anophelines captured dead was ±3 zero; in both treated villages mortality was 100% after spraying. In the 50 mg village this effect lasted for nearly four months; the blood-fed digestive stages and the parous percentages also fell to zero shortly after spraying.

The night-biting catches on human baits in the unsprayed village paralleled overall population densi-

ty with its peak from mid-August to mid-October. As expected, *A. stephensi* was also the most abundant here. In the treated villages these catches dropped to zero shortly after spraying. The night-biting catches on animals showed the same pattern, with overall higher catches of *A. stephensi* clearly indicating an animal blood preference.

The artificial pit shelter catches showing the density and parous conditions of the species outside the treated rooms reflected an undisturbed pattern throughout the season. The increased numbers even after spraying can be attributed to seasonal extension of potential breeding sites, especially due to the rice fields. The high percentage of empty and nulliparous mosquitos found can be explained by the newly hatched young mosquitos which had just emerged from the breeding habitats. Nevertheless, larval density in the treated areas per 10 dips decreased dramatically in comparison with the unsprayed village. For an indoor residual application, the break in the generation cycle achieved was dramatic. On average, a 50% density reduction could be seen every 15 days.

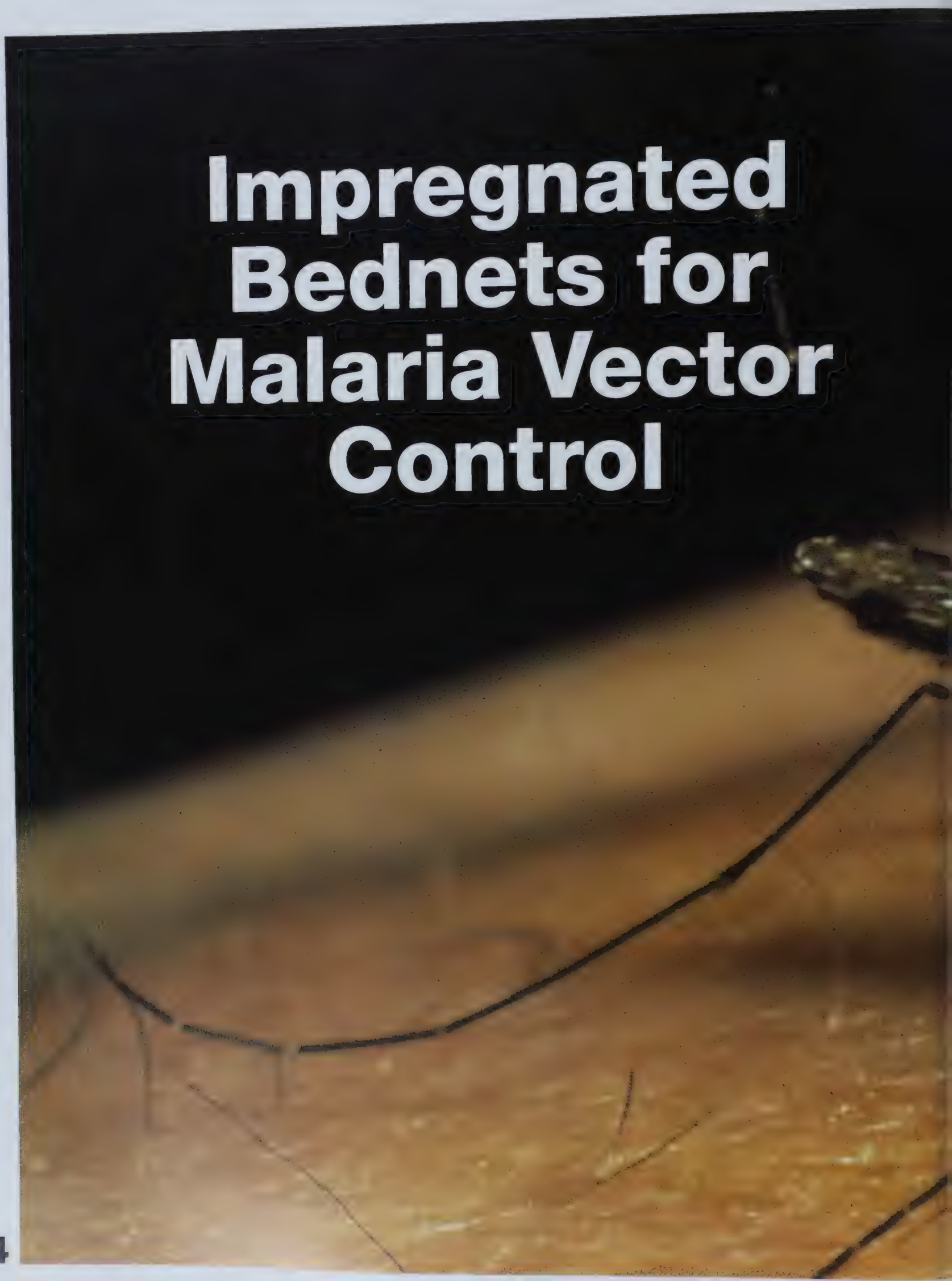
In the study area, the ceilings of the structures are made of wood and rushmat and the walls of the permanent shelters consist of raw brick and plaster. The residual effect against the main vector *A. stephensi* (laboratory bred and blood-fed) lasted a maximum of 140 days on mud surfaces, over 100 days on lime-washed surfaces and 170 days on wood (taking 75% mortality as minimum baseline). Only porous, alkaline cement degraded the effect in less than 65 days (in the area treated with 50 mg a.i./m^2).

Tab. 2: Reduction of Mosquito Night Biting Activity by Cyfluthrin Catches from Human Baits, Mamassani, South Iran, 1992
Anopheles stephensi

Month	Control area	Cyfluthrin 25 mg/m^2	Cyfluthrin 50 mg/m^2
July	10.2	19.2	6.7
August	43.4	28.2	21.2
September	29.2	6.0	3.0
October	19.9	1.5	0.7
November	6.2	0.2	2.0
December	2.0	0	0.5

An overview of all data compiled reveals highest efficacy for the indoor residual application of Cyfluthrin Wettable Powder 10 (Solfac WP 10) at application rates of 50 mg a.i./m^2 over a study period of more than 120 days.

Impregnated Bednets for Malaria Vector Control



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In the past, centrally organized programs of house spraying with residual insecticides were highly successful against malaria when targeting the *Anopheles* vectors of the disease (Photo 1). Unfortunately, however, in many countries these programs have lost momentum due to

- government spending cuts
- refusal of householders to allow spraying because nuisance insects are not killed, because they object to strangers entering their houses and because of the unsightliness or odor of the older types of insecticide which have to be used at dosages of up to 2 gm/m^2, and
- resistance of some vector populations to some insecticides and a tendency of some species not to rest long enough inside houses to pick up a lethal dose.

In view of these factors, the following question needs to be asked: Are there alternative techniques of proven effectiveness which well motivated communities would be willing and able to apply by themselves, with minimal assistance and training from central authorities?

Photo 2. Bednet installed in a house in rural Zanzibar.

Pages 24 and 25
Photo 1. Adult *Anopheles* feeding on a human arm.
Note the "tail in the air" posture which differs from *Culex* and other types of mosquito.

Impregnated nets a good method at community level

Some ideas concern new ways of attacking mosquito larvae, but in general the best policy is to attack adult *Anopheles* in the place where they do the most damage - in houses. Bednets (Photo 2) create a physical barrier against the important *Anopheles* species, most of which bite indoors, late at night. However,

mosquitos often find holes in nets or bite through them and the physical barrier provided by the nets usually needs to be supplemented by a chemical barrier consisting of a long-lasting deposit of a modern synthetic pyrethroid insecticide on the netting. These insecticides are safe for close contact with humans at the low doses required to kill mosquitos (0.01-0.2 gm/m^2), and incapacitate mosquitos before they can find holes in netting or bite through it. The sleeper inside the net attracts the mosquito to contact the net, killing the insect. Thus the net functions much like a baited trap. When used by most of the inhabitants of a village, such nets significantly reduce the number of vector insects in the village, reducing the risk of malaria for people outside nets. Examples of the protection from biting provided by impregnated intact or damaged nets, as well as their mosquito killing effect, are shown in Table 1.

An. gambiae and *funestus*				
Net	**Month of prior domestic use**	**Net treatment**	**% Fed**	**% Dead**
None	–	–	69.1	11.8
Intact	0	None	7.0	22.8
Intact	0	Cyfluthrin	1.7	46.4
Holed	15	None	61.8	14.6
Holed	15	Cyfluthrin	21.3	48.4

Table 1: Results from experimental huts at Muheza, Tanzania, on percentage of the malaria vectors found in the morning to have bloodfed (collected dead or alive) and to be dead (found fed or unfed) after nights when the sleepers were unprotected or under fresh intact or used and damaged nets with or without impregnation with 50 mg cyfluthrin/m^2.

Year	No. Cases
1980	3737
1981	4397
1982	3814
1983	6848
1984	3950
1985	5082
1986	2828
1987	2850
1988	1137
1989	899
1990	733
1991	352
1992	110
1993	58
Jan–June 1994	25

Table 2: Recorded cases of malaria in Emei County, Sichuan Province, China each year since 1980. Note that about 4,000 cases were detected annually until 1985. Treatment of bednets with deltamethrin was instituted in 1986-7 and case incidence has declined steadily since 1987. (Data kindly supplied by the County Health Authority)

This method can be applied by village communities (Photo 3) with a little guidance as to dilution of the chemical and simple safety precautions such as use of rubber gloves during the net dipping process. Pyrethroids are also effective against nuisance insects such as bedbugs, which increases communities' enthusiasm for this method.

Impressive results (see Table 2) have been achieved by treatment of bednets in China, where there is now only a limited malaria risk. Nets are already widely used and treatment of these existing nets in a house with the pyrethroid deltamethrin costs 25%-50% as much as conventional spraying of the walls and ceiling of the same house with DDT, and it is also more acceptable to householders. In Sichuan Province (Southwest China) nets are sprayed (not dipped) by spraymen recruited in the villages concerned. They are paid by the

villagers, but the chemical is provided by the provincial government antimalaria program. Up to 2.25 million nets have been treated annually since 1987. It was feared that such widespread exposure of mosquitos to pyrethroids would have selected for resistance, but collections of the two local malaria vector species made in rooms and animal sheds (Photo 4) in these areas have so far shown 100% kill with the deltamethrin dosage recommended by the World Health Organization (WHO) to detect resistance.

Excellent results have been achieved by provision of nets impregnated with cyfluthrin to a coal mining community in Orissa State, India. The impact on sickness due to malaria was clearly apparent in the reduced caseload of outpatients at the hospital.

The great majority of the child deaths due to malaria occur in Africa. However, there are encouraging reports from Gambia that a national program which treated existing bednets with the pyrethroid permethrin, carried out by primary health care personnel, significantly reduced total annual child mortality. Several WHO-supported trials are now in progress to determine whether this impressive result can be replicated elsewhere in Africa

Treated nets effective in an integrated strategy

In the humid areas of Africa with saturating levels of malaria transmission it has been shown that if the pre-existing malaria parasites are cleared from people's blood with a

Photo 3. Dipping bednets in an emulsion of permethrin. Wearing rubber gloves, the women soak the nets, wring them out like washing and then lay them out to dry on the beds over which they will be hung.

Photo 4. The author collecting *Anopheles* mosquitos in an animal shed, adjacent to a bedroom in which bednets have been treated with deltamethrin, in Sichuan Province, China. In collaboration with personnel of the Sichuan Province Anti Parasitic Disease Institute, the mosquitos were tested for deltamethrin resistance and none was found.

reliable antimalarial, the rate of re-infection is reduced by 80% or 90% in villages where impregnated bednets are in use, compared to where they are not (Fig. 1). Whether this will be sufficient to produce a sustainable reduction in the amount of malaria illness in such areas remains to be seen. Immunity to malaria is a very important factor in keeping adults in these areas relatively untroubled by malaria infection and it is important to find out whether an 80% or 90% reduction in the amount of *Anopheles* biting will be offset by a slower immunity buildup. The best long-term solution for areas of intense malaria transmission may turn out to be artificial boosting of malaria immunity with one of the malaria vaccines currently being tested or developed, and impregnated bednets to reduce the number of new infections (and infections by new strains of parasite) to a level that the boosted immune system can deal with.

Making impregated nets affordable

Meeting the cost of impregnated bednets is a problem in some communities. The United Nations Children's Fund (UNICEF) has launched programs making nets available at factory prices, which represents a major saving compared with the inflated retail price in some countries. In a Tanzanian village a proposal to establish a revolving fund to pay for insecticide for biannual re-impregnation met with a good response and agreement that those with very low incomes would be subsidized by the more fortunate. Studies in tropical urban areas much troubled by nuisance insects have shown that a considerable proportion of household income is spent on attempts to solve this problem. However, these are often by relatively costly and ineffective methods such as aerosol cans of insecticide or coils which, when lit, smolder and give off mosquito repellent smoke. It is important to find ways of helping people to understand that, in the long run, their money would be better spent if they saved up to buy enough nets for their family, along with the insecticide to impregnate the nets.

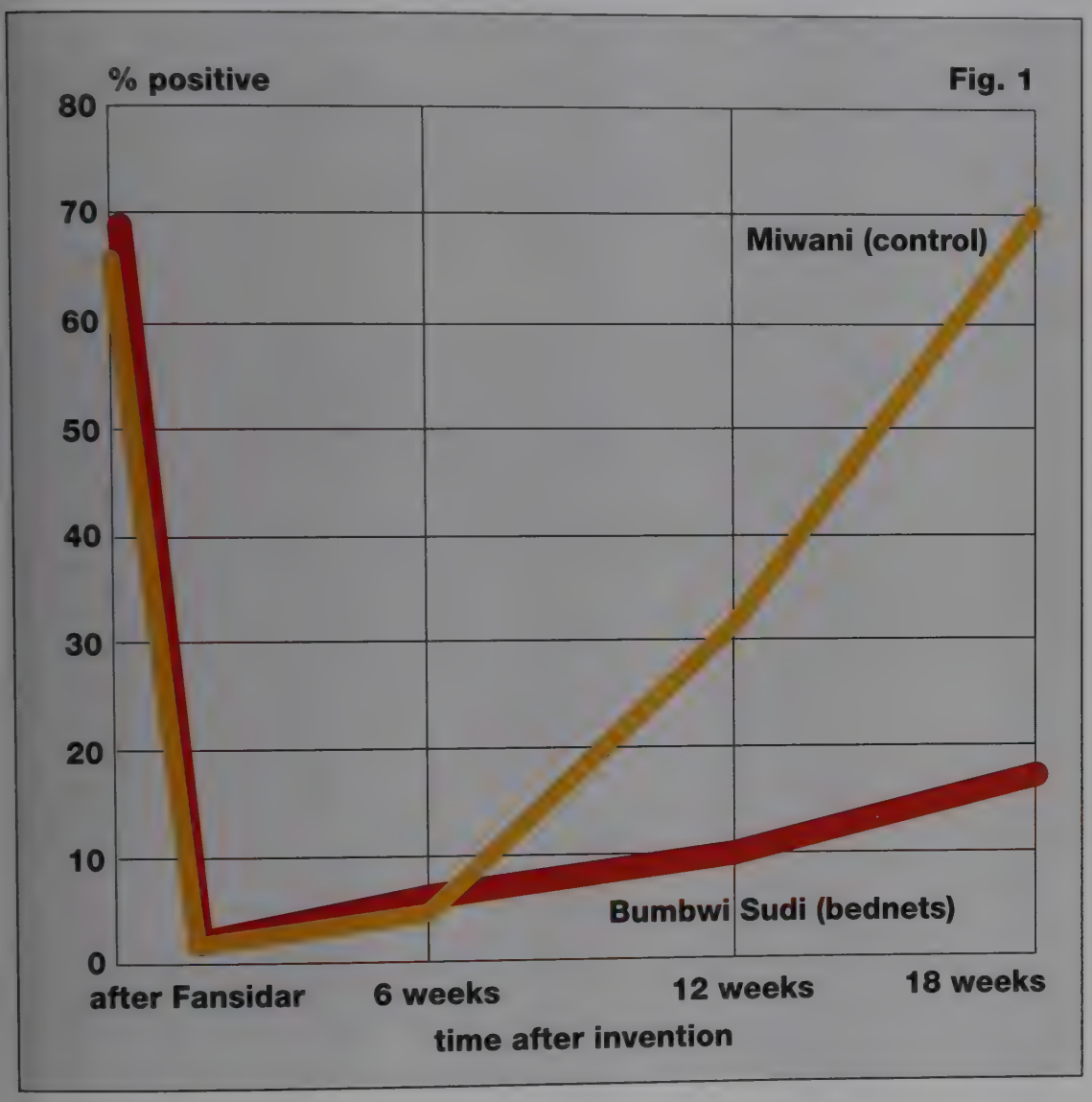

Fig. 1: Percentage of blood slides positive for malaria parasites in groups of people who were followed up at six-week intervals in two villages in an area of irrigated rice growing in Zanzibar, Tanzania. The initial malaria parasite rates of about 67% were brought down to almost zero with one dose of Fansidar. During this test in Miwani village, any nets in use were old, torn and non-insecticidal; the parasite rate had reverted to its initial level by week 18. However, in Bumbwi Sudi good quality nets freshly impregnated with permethrin had just been installed in almost all houses and the parasite rate had only reached 17% by week 18. In a trial three years earlier, Miwani had the effective nets, not Bumbwi Sudi. At that time Bumbwi Sudi showed the rapid rate of re-infection, thus confirming that it was the nets, and not some inherent difference between the villages, which were responsible for the difference in re-infection rate. (Data from A. Stich, C. Maxwell and the Zanzibar Malaria Control Program)

How Safe Are Pyrethroid-treated Mosquito Nets? An Evaluation Based on the Example of Solfac EW 050

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Introduction

The use of pyrethroid-treated mosquito nets has become an important measure in fighting and preventing malaria since an improvement in the efficacy of mosquito nets was noted. The importance of every conceivable improvement in the battle against malaria becomes clear when we consider that malaria is currently the biggest health problem worldwide. Approximately 40% of the world population lives in endemic regions and is thus exposed to the threat of malaria.

Human exposure to the preparations used cannot be completely ruled out due to the close contact that occurs when treating and using nets. As a result it is necessary to weigh the health benefits in the foreground against possible health risks associated with this malaria control strategy.

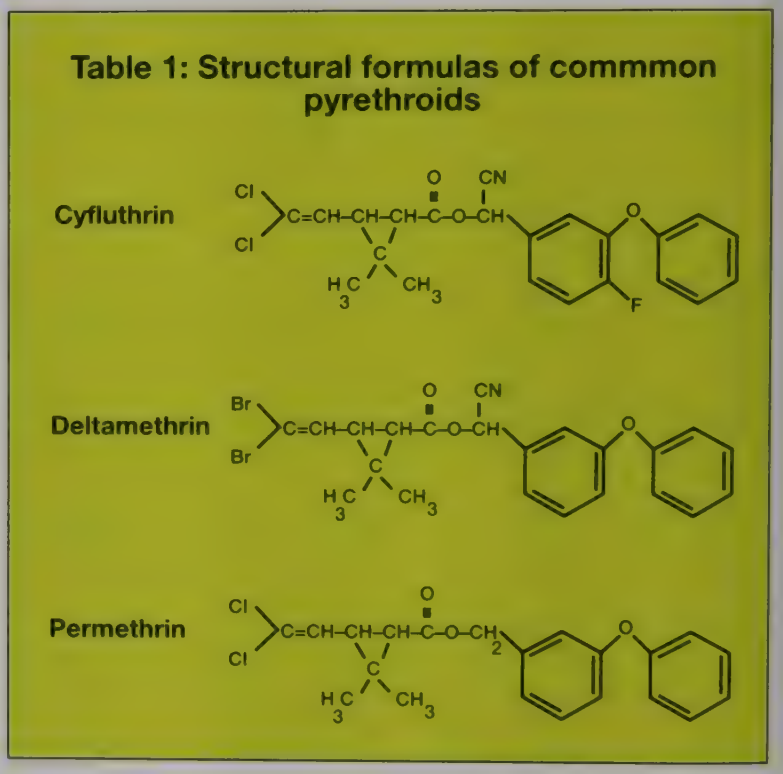
Substances used for net treatment

Pyrethroids are used for impregnation of mosquito nets in malaria prevention strategies. Pyrethroids are a family of substances originally derived from natural sources (pyrethrum extracted from chrysanthemum species, e.g. for "insect powder" made of the petals). The basic structure of the natural substances was chemically modified in order to achieve compounds with increased stability and efficacy. These compounds are characterized by extremely high effectiveness against insects coupled with low mammalian toxicity, which made them a good alternative to organochlorine insecticides (such as DDT). Pyrethroids initiate reactions in the insect's nervous system. By delaying the close of the sodium canal, the temporary sodium inflow into the cell is extended, thus resulting in membrane discharge. Short sequences of repeated nerve impulses can be observed when the so-called Type I pyrethroids (without a cyano group) are used, longer sequences in the case of Type II pyrethroids (containing an α-cyano group).

Our wealth of knowledge about these interactions, which can only be outlined here, reflects the large volume of research which has been devoted to pyrethroids. Exhaustive toxicological tests have also been carried out on the family, resulting in a sufficient data pool for risk assessment of pyrethroid use.

The most commonly used pyrethroids for impregnating mosquito nets are permethrin, deltamethrin and cyfluthrin, which have proven well suited to this purpose. Deltamethrin and cyfluthrin are α-cyano pyrethroids, while permethrin is a pyrethroid without an α-cyano group (see Table 1 for structural formulas).

Table 1: Structural formulas of commmon pyrethroids



Cyfluthrin, the active ingredient in Solfac EW 050, is under testing and evaluation by the World Health Organization (WHO). A monograph on toxicology has also been prepared (WHO, 1987). Because the studies on cyfluthrin conducted by Bayer were so comprehensive in scope, WHO was able to conduct a well-based toxicological assessment of the substance and ascertain its acceptable daily intake amount (the daily amount of a substance a human being can tolerate over a lifetime period).

Table 2 summarizes the most important cyfluthrin studies and their results. As the table shows, there are no prohibitive findings. WHO's toxicological assessment of these data revealed that a lifelong daily cyfluthrin intake of 0.02 mg/kg body weight can be considered harmless for humans. This value is referred to as ADI (acceptable daily intake).

Table 2: Important toxicological studies of cyfluthrin

Study type	Animal species	Findings/significance for humans
Acute toxicity tests following oral ingestion	Rats, mice, rabbits, dogs	Moderate acute toxicity following oral ingestion or swallowing
Acute inhalational toxicity tests	Rats	Moderate acute toxicity upon inhalation
Acute toxicity tests following dermal application	Rats	Low acute toxicity following single skin contact
Toxicity tests following repeated dermal application	Rabbits	Low toxicity following more frequent skin contact
Tests of local skin irritation and skin sensitization	Rabbits Guinea pigs	No indications of skin irritation or skin sensitization
Tests of embryo toxicity/teratogenicity and reproduction	Rats Rabbits	No indications of embryotoxicity/teratogenicity or reproduction toxicity
Mutagenicity tests	In vitro Mice	No indications of genotype-altering effects
Neurotoxicity tests	Rats	No indications of irreversible neurotoxic effects
Subchronic toxicity tests	Rats Dogs	No indications of specific organ damage
Tests of chronic toxicity and carcinogenicity	Rats Mice	No indications of carcinogenic potential

In short, cyfluthrin is a thoroughly tested substance from which a special hazard is not expected.

The following will focus on the safety of practical use of the Bayer product Solfac EW 050 (containing cyfluthrin as active ingredient) to treat mosquito nets. The two different types of potential risk concern net impregnation (skin contact) and human presence inside nets (inhalation).

Safety of net impregnation

When nets are treated following safety precautions, no actual skin contact takes place, or at least larger-scale exposure of skin surfaces is prevented as gloves are worn to eliminate close contact. However, skin exposure is theoretically possible because gloves might be left off out of negligence or for convenience, especially when the treatment is done by laymen. Skin contact is the main danger in potential exposure of this type; inhalational exposure is insignificant due to the fact that nets are impregnated outside.

Toxicological studies of cyfluthrin included investigation of the toxicity of dermal as well as oral application. Research findings are available for single and multiple dermal administration of cyfluthrin to laboratory animals.

In these studies, the test sample is applied to a shaven area of the skin which is covered by a dressing so that the substance can be absorbed over a longer period of time (24 hours) and have a chance to take effect. Afterwards the animals are observed for possible side effects. Although dermal exposure would never occur under such conditions in practice, the laboratory conditions are designed to be as extreme as possible to guarantee high safety standards for human risk assessment.

In one study of acute dermal toxicity, rats were administered a maximum dose of 5,000 mg/kg body weight, which was left on the skin for 24 hours under an occlusive dressing. The rats tolerated this very high dosage without clinical signs (Heimann, 1986). These findings

show that dermal contact can be seen as posing no acute potential hazards to humans.

The substance was applied repeatedly to the skin of rabbits, considered more permeable and more sensitive than human skin, for five days a week over a period of three weeks in doses of 50 and 250 mg/kg body weight. The highest test dosage of 250 mg/kg body weight caused no effects, thus counting as the no-observed-effect level (NOEL) (Flucke et al, 1980 a).

The recommended dosage of Solfac EW 050 (50 g cyfluthrin/l preparation) for treating mosquito nets is 1 ml of preparation/m^2 net, e.g. 10 ml, containing 500 mg cyfluthrin for a standard-size net measuring 10 m^2. If the entire application formula were to come into contact with the skin (which would be virtually impossible), theoretical maximum exposure would be 500 mg of the active ingredient. Given a body weight of 60 kg, this would constitute a maximum dose of approximately 8 mg/kg body weight. Thus there is a safety margin of 625 for single exposure and approximately 31 for multiple exposures between the NOELs and this theoretical dose (Table 3).

Due to this large safety margin and the fact that exposure time for humans would never match that for the laboratory animals, treating a net (once or repeatedly) poses no detectable dermal poisoning risk to humans.

Local skin effects can likewise be ruled out, as the findings of other studies demonstrate.In studies examining skin irritation potential, cyfluthrin was applied to rabbits, whose skin is likewise considered very sensitive for these purposes, under four-hour occlusive dressings. Checks for local reactions were then conducted at set intervals. Cyfluthrin was not shown to cause any skin irritation in these studies (Flucke et al, 1980 b; Iyatomi et al, 1982).

In sensitization tests done on guinea pigs, cyfluthrin was examined as regards its cutaneous sensitization potential. After an initial induction treatment followed by a pause, cyfluthrin was re-applied to trigger possible sensitization. After the follow-up application, the animals were observed for skin reactions.

These cyfluthrin studies showed no potential for skin sensitization (Mihail, 1981a,b; Iyatomi, 1983).

To sum up, any skin exposure which might occur during net treatment will not result in either skin irritation or sensitization.

This was also confirmed by studies using human test subjects. Subjects who were administered cyfluthrin in a dose of 150 mg/m^2 skin on a skin surface measuring 4 x 4 cm^2 showed no skin reactions (Ippen, 1989).

Overall, the relevant toxicological studies did not indicate that mosquito net treatment with Solfac EW 050 poses a potential threat to humans.

Table 3: Comparison of possible dermal exposure doses and toxicologically harmless doses (NOEL)

Study	NOEL		Exposure dose	Safety factor
Acute dermal	5,000 mg/kg body weight	≤	8 mg/kg body weight	≥ 625
Repeated application	250 mg/kg body weight	≤	8 mg/kg body weight	≥ 31

Safety of net use

As the possibility of inhalational intake dominates this rubric, safety assessments focus on toxicity studies of inhalational intake of the substance (via the respiratory tract) using laboratory animals.

In these studies animals (generally rats) are exposed to the substance in dust or aerosol form by means of special test equipment (see Illustration 1). Cyfluthrin was examined as regards acute, subacute and subchronic inhalational toxicity.

An acute inhalational toxicity study (inhalation period: four hours) determined the LC50 (concentration at which 50% of animals die) for cyfluthrin to be 405 mg/m^3. The no-observed-effect level was also ascertained. The animals were able to tolerate an air concentration of 5.2 mg/m^3 without harmful effects (Pauluhn, 1987).

Findings are available for cyfluthrin studies lasting four weeks (subacute study) and 13 weeks (subchronic study). In both study models the laboratory animals were inhalationally exposed to the substance six hours a day, five days a week.

In the four-week study, the rats were exposed to cyfluthrin concentrations of 0.44, 6.0 and 46.6 mg/m^3. At 6.0 mg/m^3 and more, the animals showed changes in body weight as well as reflex bradypnea (reflexive retardation of respiration), which also resulted in hypothermia. The highest-dose group developed as-yet non-specific symptoms. The dose of 0.44 mg/m^3 proved to be the NOEL (Pauluhn, 1989).

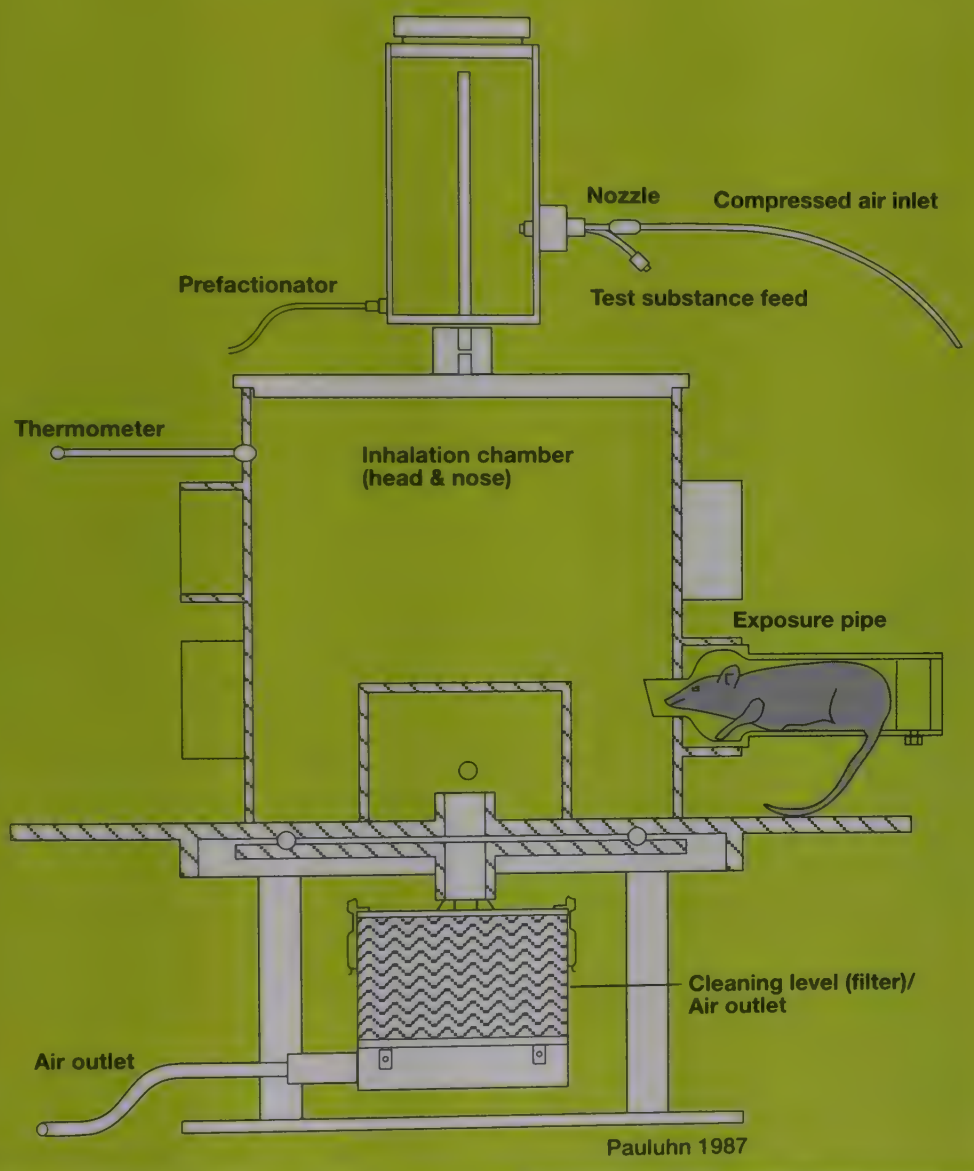
In a similar study conducted over a period of 13 weeks with doses of 0.09, 0.71 and 4.5 mg/m^3, only slight changes in body weight could be detected starting at 0.71 mg/m^3. The low dose of 0.09 mg/m^3 was established as the NOEL (Pauluhn, 1984).

Overall, these inhalational toxicity studies showed that cyfluthrin

merely caused local, functional respiratory tract effects, not specific damage to other organ systems. The most sensitive effect proved to be reflex bradypnea induced by sensory irritation. This effect should be interpreted as the rats' defense mechanism against inhalation of substances causing sensory irritation, not damage per se. The decisive trigger of this local effect is not cumulative dosage, but rather the concentration of the active ingredient. A special study using rats revealed a no-effect level at a concentration of 0.5 mg/m³ (Pauluhn, 1988). It is generally agreed (Nielsen and Vinggard, 1988) that 20% of this value, i.e. 0.1 mg/m³, can be viewed as the maximum tolerable value.

An additional safety factor of 10 is used when transferring this value from animals to humans, which means that a cyfluthrin concentration of 0.01 mg/m³, which is even below the NOELs established in the inhalation studies, can be considered harmless to humans and therefore a tolerable dosage.

Illus. 1: Schematic depiction of an inhalational toxicity test



Cyfluthrin concentration in room air after installation of treated nets

A practical model trial was conducted to measure active ingredient concentrations after treated nets were set up (Riegner, 1994). A net measuring 9.5 m² was impregnated with 50 mg of cyfluthrin / m². The net was hung up in an enclosed, unventilated room simulating tropical climate conditions (temperature: 29-30°C; relative air humidity: 60%-84%). The room measured 12.8 m² with a ceiling height of 2.86 m (vol : 36.7 m³). At an intake rate of 2 l air/minute, samples were taken in each case over a six-hour period inside (10 cm) and outside (10 cm and 1 m) the net and analyzed for cyfluthrin. The detection limit of the analysis method was 0.000010 mg/m³; the lowest level for quantitatively accurate findings was 0.000050 mg/m³ air.

The amount of cyfluthrin measured in the air was slight, just above the detection level. The mean value was 0.000021-0.000038 mg/m³ (Illus. 2). Concentrations inside the net were somewhat higher than outside, which can be attributed to the lower exchange rate inside the net.

Similar results came from a smaller-scale laboratory test in which a treated net measuring 30 cm² was suspended in a flow chamber (15 l). The mean air concentrations were determined to be 0.000021 mg/m³.

These studies show that concentrations of the active ingredient can be detected in rooms where treated nets have been installed, but that these concentrations are very low, just slightly above the detection level for the analysis method used.

Much more important for safety assessment purposes is the fact that all values lie significantly under the above-mentioned tolerable dose of 0.01 mg/m³ considered harmless for humans. A safety margin of 182 separates this value from the highest concentration measured inside the net (0.000055 mg/m³); average substance concentrations inside and outside the net indicate safety margins of approximately 263 to 476 (Table 4). These constitute considerable safety allowances (see Illustration 3 for graphic depiction).

This means that the malaria control preparations used for net treat-

ment are not expected to place persons spending time inside the nets or in rooms containing them at increased risk.

Risk assessment conclusions

As a result of close human contact with the preparation during net treatment and later inside the nets, the possibility of exposure cannot be excluded when Solfac EW 050 with active ingredient cyfluthrin is used to treat mosquito nets. For this reason it was evaluated whether these health protection measures for malaria control pose possible health risks to humans.

Based on the toxicological profile of cyfluthrin, the substance showed no a priori indications of specific risk potential.

In addition, examination of all aspects of mosquito net treatment, taking into account all relevant toxicological study findings, indicated no potential risks to persons treating nets with Solfac EW 050. The safety margin between the NOELs and the maximum dermal exposure theoretically possible is extremely large for net treatment resulting in accidental dermal exposure, even in a worst case scenario.

The same goes for persons spending time inside nets or in rooms containing nets. Mosquito nets treated with malaria control formulas were not shown to place humans at increased risk. As a practical model trial showed, there are very high safety margins between the tolerable value of 0.01 mg/m³ yielded by special inhalational toxicity studies and expected substance concentrations, even though worst case conditions were certainly involved. The allowances ranged from 182 in the worst case (maximum value) to around 263 - 476, based on average concentrations in the air inside and outside nets. Even more favorable conditions and higher safety margins can be expected in practice as most houses and rooms in the affected regions are not completely enclosed, making for significantly better ventilation than in the enclosed space used in the model study described. In addition, in practice the nets are usually rolled up each morning and re-hung again at night, preventing substance concentrations from accumulating in the air of the rooms. Thus the concentrations likely in practice are significantly below the concentrations measured in the model study and used as a basis for risk assessment.

This positive assessment is also confirmed by the findings of practical tests using Solfac EW 050. No negative effects of treating and using nets have to date been determined by the many tests conducted using Solfac EW 050.

In conclusion, it is clear that use of mosquito nets treated with Solfac EW 050 for improved protection against malaria does not place humans at increased risk - an unequivocal confirmation of the health benefits provided by this malaria control method.

Illus. 2: Cyfluthrin concentrations measured in room (mg/m³) in a practical test

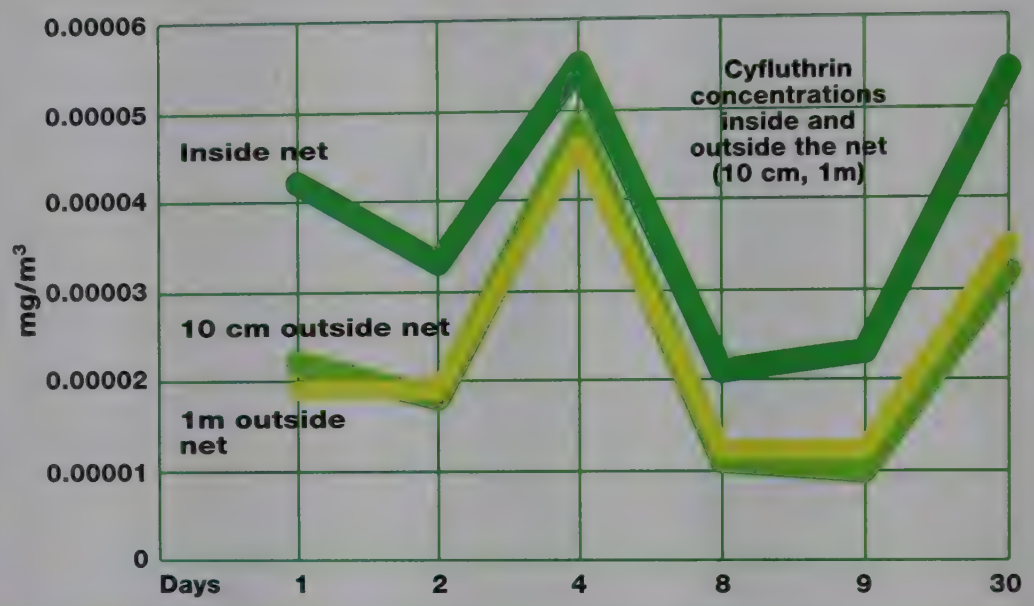


Table 4: Comparison of possible inhalational exposure doses and tolerable doses for humans

Study	NOEL	20% of NOEL	Tolerable dose*
Sensory irritation effect (rats)	0.5 mg/m³	0.1 mg/m³	0.01 mg/m³

*Based on a conversion factor of 10 (for transfering from animals to humans)

Tolerable dose*	Exposure dose	Safety margins
0.01 mg/m³	0.000055 mg/m³ (highest value inside net)	182
	0.000038 mg/m³ (mean value inside net)	263
	0.000021 mg/m³ (mean value outside net)	476

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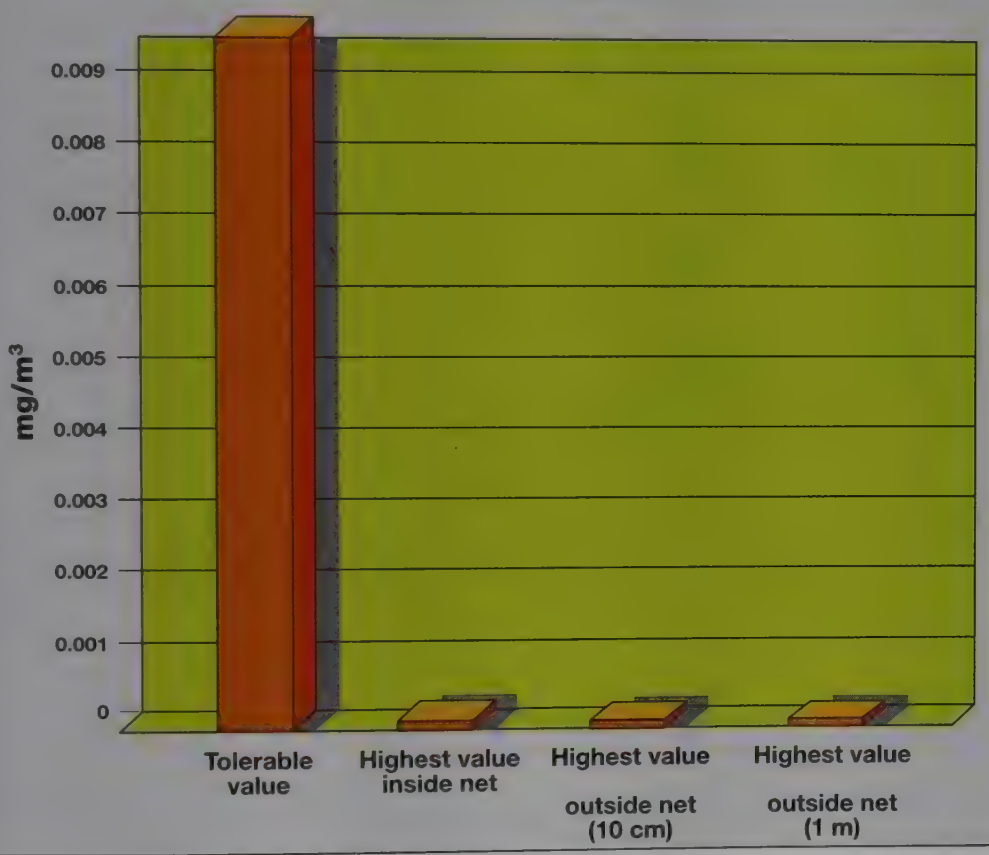
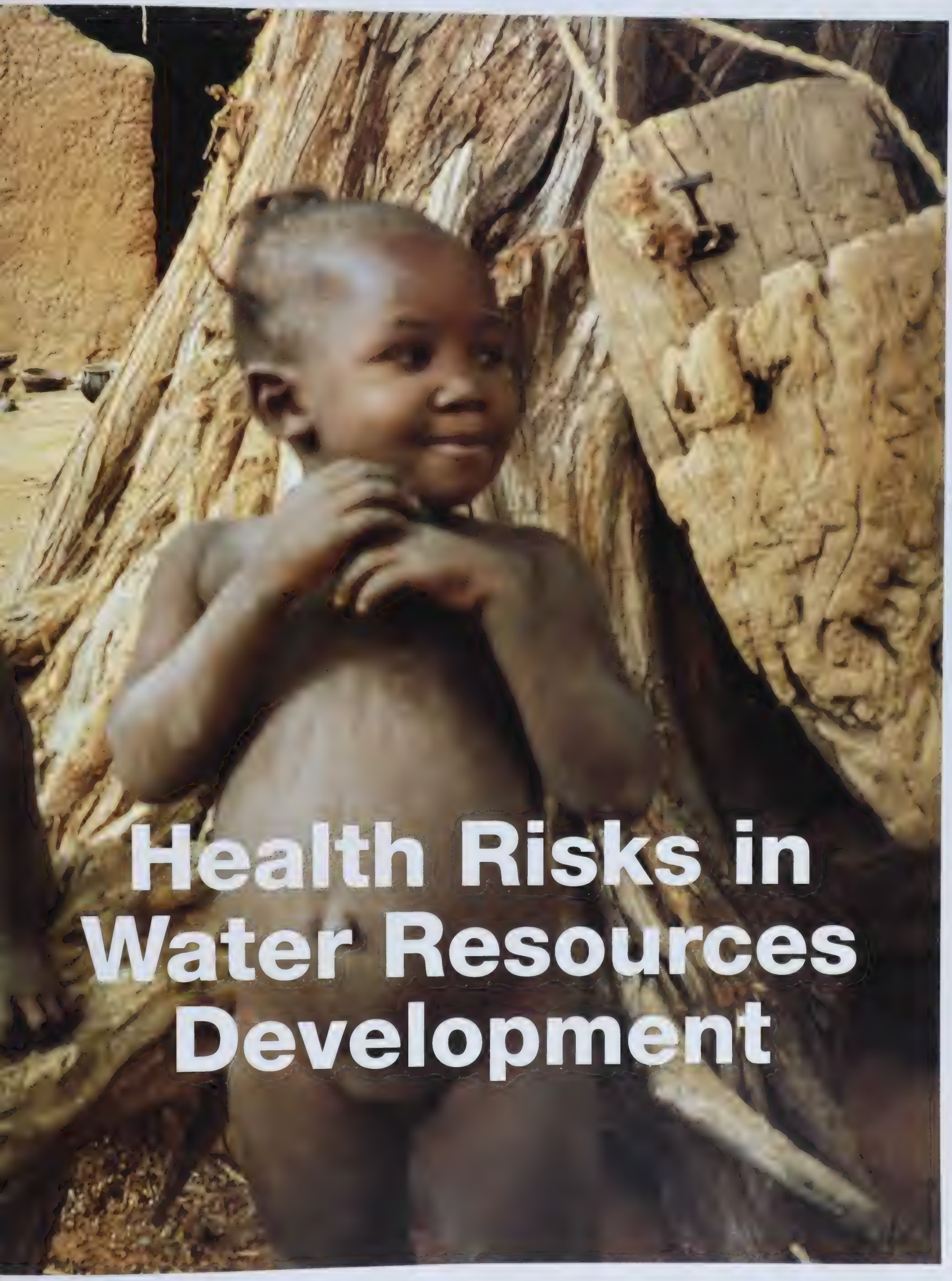
Illus. 3: Comparison of highest cyfluthrin concentrations measured and the tolerable dose/concentration for humans (inhalation)





Health Risks in Water Resources Development

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Drought, hunger and the need for water resources development

The total population of the developing regions of the world, which was 3.7 billion (10^9) in 1985, may rise to 6.8 billion by the year 2025. At the conclusion of this 40-year period, developing regions will account for 83% of the world's population. These areas, principally tropical developing countries, face a combined burden of rapid population growth, recurrent food shortages, underemployment, deficits in family income, and chronic inability to effect structural changes in the economy.

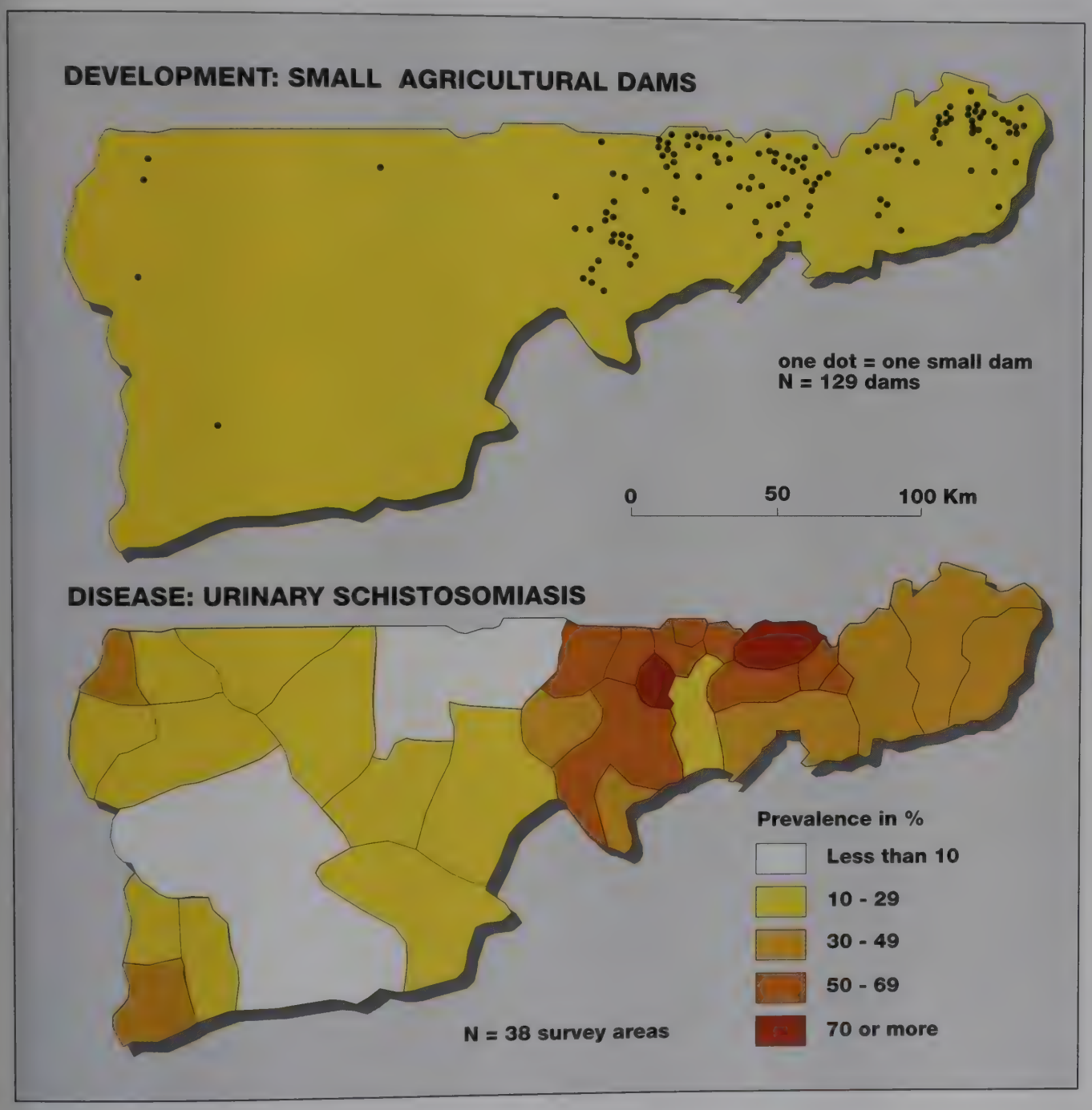
Such distressing circumstances are at their worst in peripheral and remote rural areas, zones of seasonal rainfall where the dry season may be of three to nine months' duration, with superposed irregular rains and drought. These are the most critical localities for human survival, under pressure of crop failure, endemic malnutrition, hunger and starvation.

The appropriate developmental response - as widely agreed among UN agencies and participating governments - is the harnessing of water resources. In fact, water resources development is the essential primary strategy for increasing total food production, improving livestock health and human nutrition, and generating

disposable income. The undeniable logic for water resources development rests on renewable use of resources, sustained yields, ecosystem stability and improved human welfare. Tropical developing countries with high temperatures, high evaporation rates and variable rainfall stand to benefit enormously from water impoundment and irrigation projects. Enhanced by improved management and the technologies of the "green revolution," crop yields greatly increase. Why then should medical authorities and public health planners be so apprehensive about water resources developments which, at first glance, are potentially so beneficial to human health?

Clear link between development and disease

The answer to the above question is that irrigation projects commonly produce elevated levels of parasitic diseases, to the extent that human illness seems to be the price paid for economic development. The predominant threats to human health in irrigation projects are schistosomiasis (bilharziasis), lymphatic filariasis (elephantiasis) and malaria, with Japanese encephalitis and dengue less widespread. The scale of the threat in less developed countries is enormous: schistosomiasis is endemic in 74 countries, with 200 million persons infected and 600 million at risk; malaria is endemic in some 93 countries, with 270 to 480 million cases in Africa alone; lymphatic filariasis is found in 76 countries, with 78 million cases and 752 million of the population exposed. Japanese encephalitis is also strongly associated with development activity but less data are available.



The distribution of small agricultural dams (upper map) closely corresponds with high prevalence of schistosomiasis (lower map) in the lower regions of Ghana. Construction of the dams increased the prevalence of urinary schistosomiasis from 17% to 51% (Hunter, 1981).

Exacerbation of these diseases, their further spread and intensification by irrigation projects exact a heavy toll on human health, the cost of which must be seen as offsetting some of the social and economic benefits of development planning activities. The disease burdens include death and loss of years of expected life, chronic morbidity and disability, absenteeism, and reduced agricultural productivity. Specifically, heavy infections of schistosomiasis (the blood fluke disease) produce daily blood loss in stool and urine over a period of years, lesions of the genito-urinary system including calcification of the bladder, gastrointestinal damage, impairment of liver function, and hepatosplenomegaly. The major forms of schistosomiasis are *Schistosoma haematobium*, *S. mansoni* and *S. japonicum*; each is associated with specific snail species.

Clouds of mosquitos breeding in stagnant water at poorly managed irrigation projects can raise the intensity of malaria and lymphatic filariasis to intolerable levels. The most lethal form of malaria is caused by *Plasmodium falciparum* and is sometimes known as cerebral malaria. Child death is common. Even with an elevated immune status acquired through community exposure, plus genetic protection afforded by abnormal hemoglobins (e.g. "S" and "C"), recurrent acute episodes of malaria result in heavy work losses among adults, pregnancy complications, and chronic depletion of energy and sense of well-being. The rise of chloroquine-resistant malaria further compounds the role of "irrigation malaria."

Rocky island in rice irrigation project. Rice prospers during long dry season.

Dry season tomatoes offer a profitable supplement to rice cropping. Painted slogans identify ownership of crates. This one reads: Who is free?

This pregnant woman has a non-lactating right breast due to filariasis. Her two children were fed solely on the left breast.

Woman with typical elephantiasis - will walk many kilometers to market.

Filarial swelling of right wrist and both legs. Acute hyperplasia of foot. She is married and has two children.

Lymphatic filariasis, sometimes described as elephantiasis and caused by *Wuchereria bancrofti* and *Brugia malayi*, is a permanently disabling and acutely disfiguring disease. Its effects arise through obstruction of lymph circulation initially caused by mosquito-transmitted parasitic worms. Neither gender is spared the indignity of this disease which impartially afflicts hands, legs, feet, breast, vulva and scrotum. The disease is endemic in many tropical countries of Asia, the Western Pacific, Africa and Latin America, particularly in urban and semi-urban townships where mosquito breeding is heavy in sullage water surfaces and at irrigation and agricultural development projects.

Japanese encephalitis, a mosquito-borne arbovirus disease, causes inflammation of the brain, often with fatal complications. Dengue and dengue hemorrhagic fever (DHF) are mosquito-borne viral diseases antigenically related to yellow fever virus. There are four district viruses - dengue 1 through 4 - which cause classic dengue fever in humans. No cross-protection exists between these viruses; an individual who has recovered from a dengue 1 infection remains susceptible to infections by the other dengue viruses. There is strong evidence that the risk of the severe form of DHF is substantially greater among persons suffering from a second dengue infection.

The pathology of these diseases and the human costs they extract should not be underestimated when cost-benefit balances are being assessed in water development planning.

Reasons for the "disease and development" phenomenon are clear enough. Year-round water storage and water utilization in agriculture enrich the habitat and increase the populations of mosquitos and snails that serve as vectors for parasitic diseases. Another factor promoting disease transmission is extended water contact in and around the irrigation projects by workers, their families and neighbors. Thus initial low-level endemicity can be transformed into hyperendemicity. Successful projects also encourage migrations of people in search of work, including disease carriers who may further "seed" and intensify transmission.

Documentary evidence on increases of disease in water resources development is abundant. Projects to grow cotton, sugar cane or rice on a large industrial scale are commonplace. The Sudan Gezira-Managil Cotton Project provides an outstand-

ing example. Following construction of the Sennar Dam in 1925, the prevalence of urinary schistosomiasis rose from less than 1% to 21% among adults and 45% among children in 1952. Intestinal schistosomiasis increased to a prevalence level of 73% by the mid-1970's despite control efforts. Additional projects in the Sudan, such as the Blue Nile Rahad scheme, in 1988 produced levels of 9% to 10% for both urinary and intestinal schistosomiasis despite strong health-protective interventions.

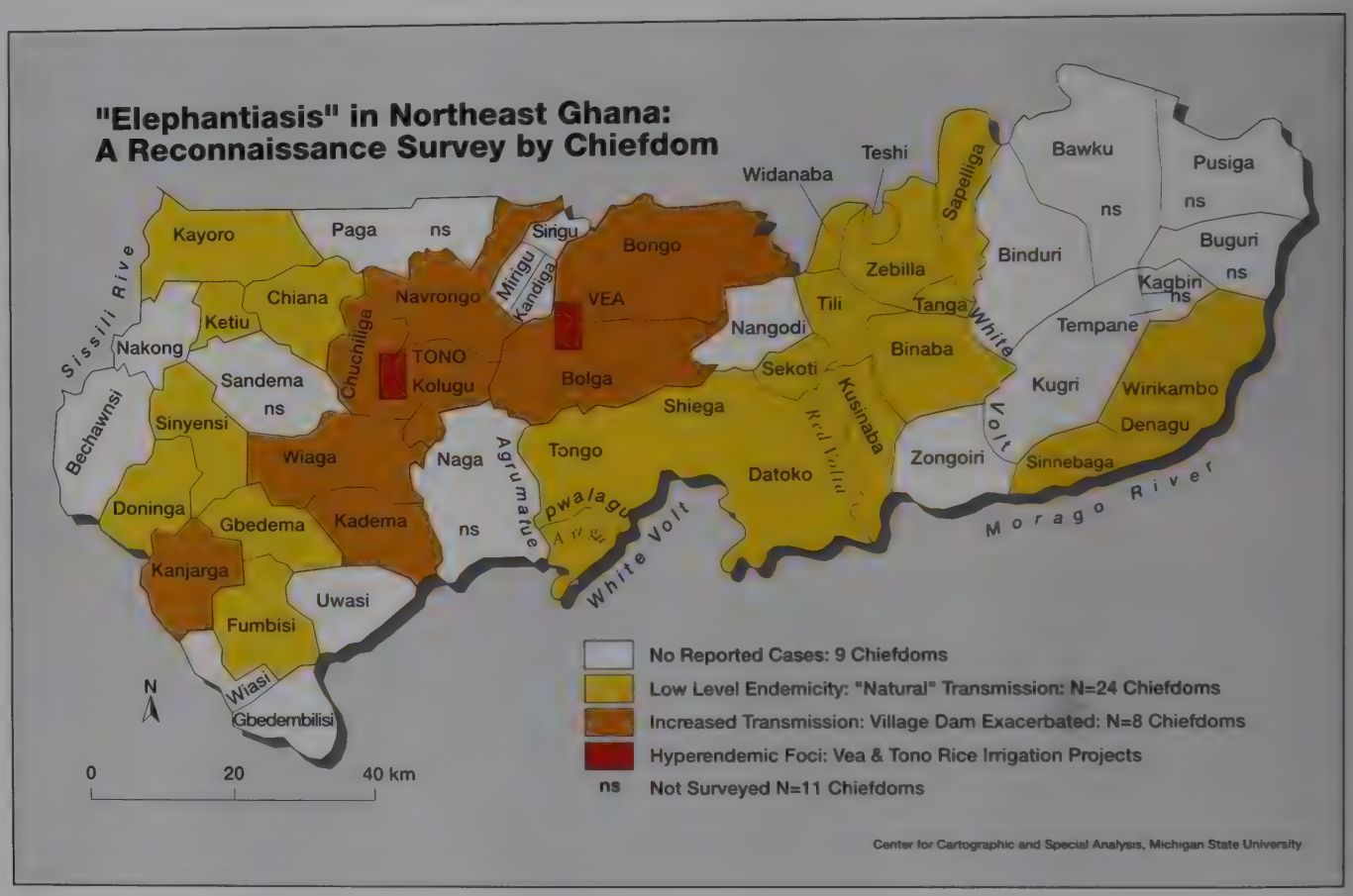
A third example illuminates the ecological complexity and disease consequences of water resources development. Following completion of the Aswan High Dam, in the Nile valley of Egypt, seasonal flood-agriculture was replaced by perennial multiple cropping. Disease intensification ensued and, in addition, the predominant snail vectors changed from *Bulinus* to *Biomphalaria* species, resulting in a relative decline of urinary schistosomiasis and an increase of the gastrointestinal form of the disease. This increase in total disease burden and the accompanying clinical changes were unforeseen.

Throughout the tropical developing world, agricultural projects continue by necessity to utilize water resources development, both large- and small-scale. Paradoxically, their economic success often results in disease intensification which increases the load on already overtaxed public health authorities.

Burdens on health care authorities

Public health authorities, especially in tropical rural areas, face numerous burdens that collectively impede their efforts in disease control. These are:

- An insufficiency or quantum lack of financial support. For example, US$2-$4 per capita per year amounts to very little when spread against a nation's needs.



The disease (lymphatic filariasis, elephantiasis) is generally scattered and sporadic at a low level of endemicity in northeast Ghana. However, there is increased transmission around village dams and hyperendemicity in 16 villages around the two rice irrigation projects (Hunter, 1992).

Another example is Akosombo Dam in Ghana, constructed to provide hydroelectricity for industrial power, aluminium smelting and rural and urban electrification. The newly formed Lake Volta offered abundant harvest of fish for a protein-deprived population. It also created hyperendemic urinary schistosomiasis with prevalences of 100% among high-risk lakeshore groups.

- A bias, even misappropriation, of health budgets for urban areas, with consequent rural neglect. In most countries, a map of physicians is a map of the towns, not a map of rural health care needs. Although they are the majority, the rural poor are politically voiceless and underserved by health care systems.

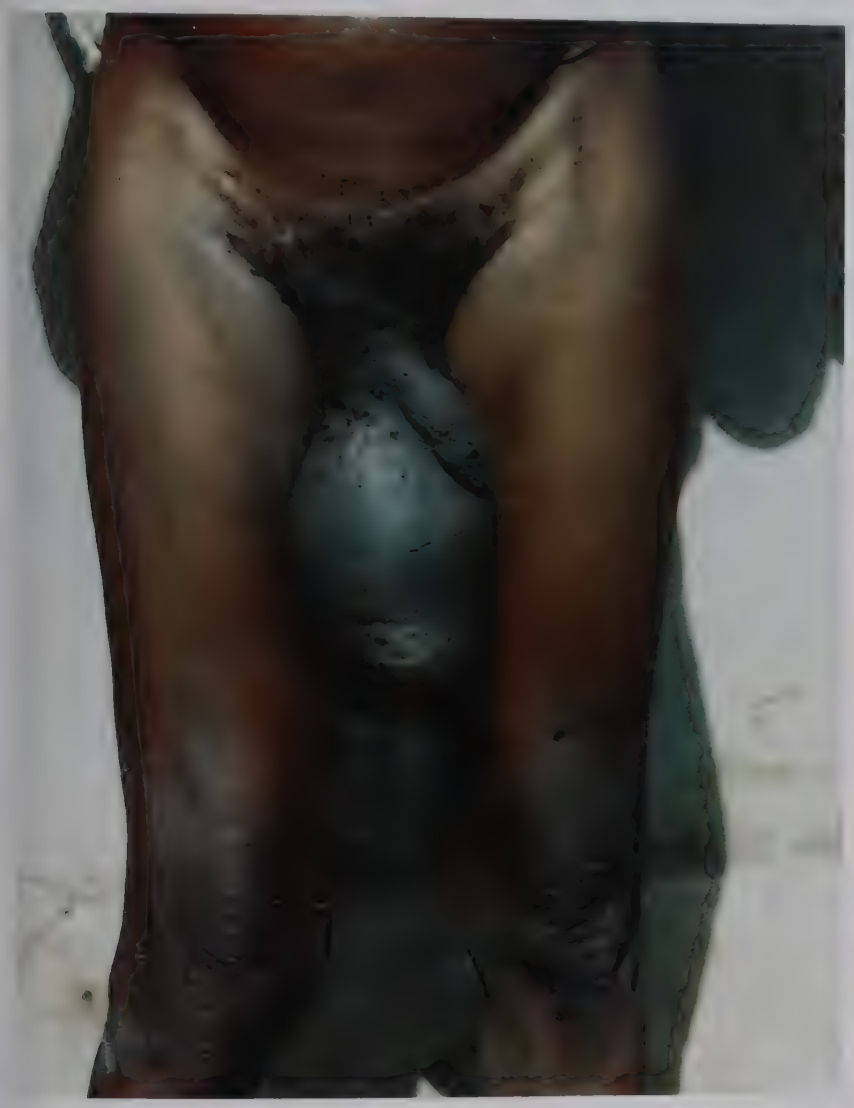
- A critical feature of the health budget dilemma is the high proportion of fixed costs, mainly linked with personnel salaries. When these obligations are met, virtually no discretionary budget remains for

emergency responses or preventive outreach capability. The absence of vehicular support for endemic outbreaks and rural vaccination programs has tragic consequences for child survival.

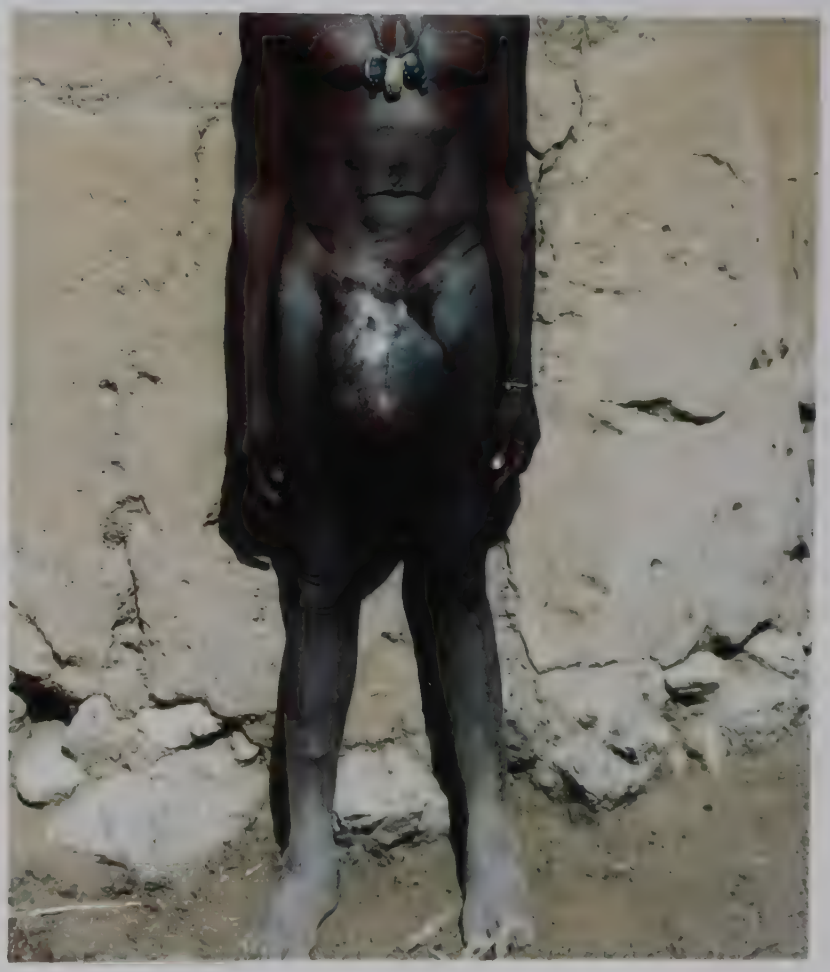
● The emergence and spread of resistance to "drugs of choice" - for so long the reliable allies of the public health worker - now demand multiple drug therapies (MDT). MDTs are much more complicated and expensive and require more personnel and infrastructural support. Again, it is the rural areas that suffer the most acute problems.

● Continuing high birth rates inexorably add to the "population-at-risk" in rural areas, which of course means that there are more people to care for, a greater demand for preventive services, and an expanding need for treatment of the endemic masses and vigilant surveillance against epidemic outbreaks.

With scarce resources, the problems of health care authorities in rural developing areas are legion and intransigent, if not intractable. Why, then, do we allow the "disease-and-development" syndrome to proceed unchecked - thus further adding to the public health burden - if indeed such disease increases are preventable?



Irrigation worker with scrotal enlargement.



"Hanging groin" complicates scrotal enlargement. Evidence of past surgical drainage.

Responsibility of technical assistance and funding agencies

Driven by legitimate needs for increased food supplies and income, water resources development projects principally derive from the technical and financial initiatives of international development agencies. These are powerful extrinsic forces in the developing world. They include the World Bank, regional banks (e.g. African Bank), the United Nations Development Programme (UNDP) and unilateral agencies of the United States of America, France, Germany, the United Kingdom, Sweden, Saudi Arabia, Japan, and many other countries. Collectively, their financial support and technical planning give greater momentum to the global rate of dam and irrigation development.

Unfortunately, very few measures for disease prevention are included in the initial economic planning and engineering design. Indeed, de-

spite sympathetic expressions of concern, line-item, recurring budget allocations for disease control are excluded from the basic economic plans. This means that an outside development agency can enter a region, build 100 small, village-scale dams - thereby tripling the rate of urinary schistosomiasis - and then figuratively walk away, leaving a beleaguered, underfinanced and unprepared ministry of health to cope with the disease explosion. What are then the costs of " development" when, decades later, chronic blood loss and anemia, calcified bladders and genito-urinary lesions have to be taken into account? In the long run, it is inefficient and unethical to ignore the human health costs of bad planning; and yet, nearly 70 years after the lessons of the Sennar Dam, planning malpractice continues at the expense of health maintenance.

The future: Planning and cooperation

Today there is a large body of knowledge available through the World Health Organization on tropical disease control which, if properly applied, can secure much better treatment and prevention of "irrigation" disease. Strategies include screening and treatment of carriers, new treatment schedules, re-organized local-level services, vector control measures (e.g. anti-snail and anti-mosquito), engineering designs and practices, knowledge of human behavior and how to change it if necessary, and community organization. All of these must be considered ab initio and included in the original design, with assured funding provided by the technical assistance agencies.

Basically, the role of officials at the ministries of health must be transformed from one of detachment and passive, after-the-fact recognition of the health consequences of national planning ventures from which they have essentially been excluded. In future, they must be aggressive participants in intersectoral negotiations, co-equals of the agronomic and economic planning sectors. Above all, foreign technical and financial assistance agencies should accept fiscal responsibility for the minimization of disease effects created by water resources development projects.

The village dam stores precious water in dry season but can transmit schistosomiasis and Guinea worm disease.

Boys playing in dam; distended abdomen suggests hepatosplenomegaly of schistosomal origin.

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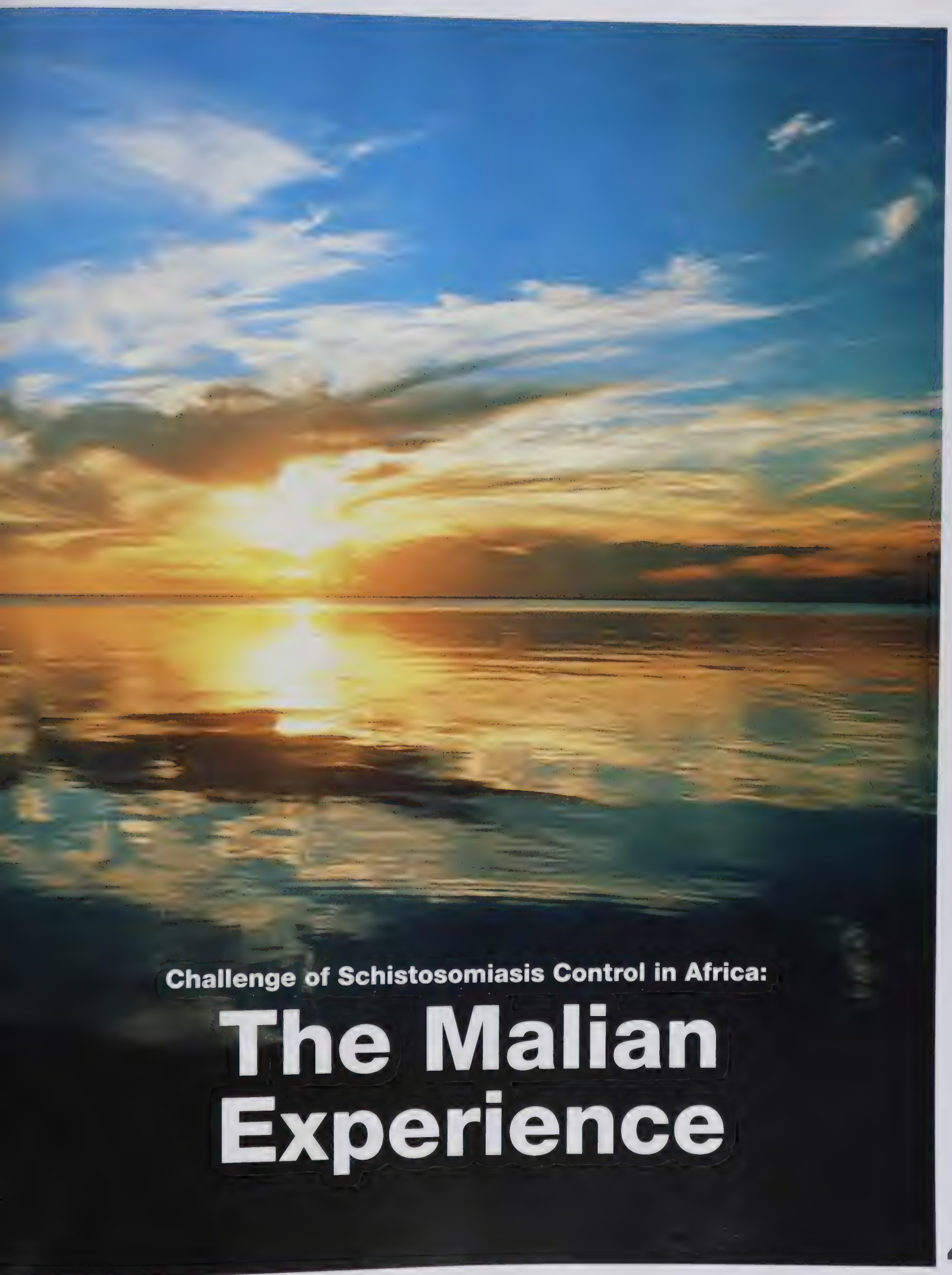

Challenge of Schistosomiasis Control in Africa:

The Malian Experience

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The National Schistosomiasis Control Program in Mali was initiated by the German Agency for Technical Cooperation (GTZ) in 1982. Now in the process of expansion, the program represents a "new generation" of schistosomiasis control activities in Africa - fully qualified and competent national staff, national training activities, decentralized delivery of control, and self-reliance. This undertaking confirms the potential for control in all endemic countries, given governmental support and provision of financial resources.

An expanding man-made disease

Mali is a land-locked country lying between latitudes 11 and 25 degrees North, with a diverse physical environment. The Malian economy relies heavily on agriculture. Dry farming of mainly millet, maize and peanuts during the rainy season is common practice in most of the country. But sufficient rain is crucial, thus there is a constant fear of drought. This is why, as in most African countries, the Malian government and population have been making strenuous efforts to build as many dams as possible to make more water available for most of the year. To this end, big and small dams have been built across the two important rivers (Niger and Senegal) and their tributaries.

All water bodies are potentially suitable for:

- rice cultivation in perennial irrigation areas (Office du Niger, Baguineda, not forgetting the "Delta Intérieur" and numerous surrounding natural lakes);

- vegetable growing in small dam areas on the Plateau Dogon;

● fishing and gathering reeds, plants, etc. around artificial lakes (Selingue and Manantali) and along rivers.

As a result, economic, domestic and recreational activities with prolonged water contact have dramatically increased. So has schistosomiasis transmission.

Two species of schistosomes affecting man are endemic in Mali - *Schistosoma haematobium* and *S. mansoni*. The presence of *S. intercalatum*, reported by Corachan et al. (1987; 1992), has yet to be confirmed.

S. haematobium is endemic in all parts of the country including urban areas (a prevalence of 50% to 82% is recorded in schools in Bamako). Very high prevalence has been recorded along the Senegal and Niger rivers and their tributaries (50% to 95% in the general population). But the most significant transmission occurs in dams and irrigated areas (Office du Niger, Plateau Dogon, Selingue, Manantali), where an overall prevalence of 80% to 90% for schistosome infections has commonly been reported.

As in most endemic areas, age-specific prevalence and intensity curves follow the classic pattern, with peak prevalence among the 7 to 14-year age group and a steady decrease after the second decade of life. The impact of praziquantel, which has consistently been effective in curing more than 90% of infected individuals, has always been of short duration because of rapid reinfection.

Based on data collected in 40 villages, Graph 1 illustrates the age-specific prevalence of schistosome infection with *S. haematobium* and/or *S. mansoni* in Office du Niger and the level of reinfection one year after treatment.

Establishment of Mali's schistosomiasis control program

The small dam building project funded by GTZ in the Plateau Dogon region in the 1970's led to a major improvement in vegetable growing, but also to substantial increase in the prevalence of urinary schistosomiasis in surrounding villages (Pleah, 1976). It was recommended that action be taken in order to prevent further spread of infection. In 1978 the dam construction project was complemented by a schistosomiasis control program.

Starting in 1982, this program was extended to all major irrigation and dam areas and became a national program, with ongoing GTZ assistance in financing and expertise (Brinkmann et al., 1988a). Major tasks included definition of high, moderate and low transmission areas and evaluation of cost-effective control measures.

Madsen et al. (1986) showed that focal molluscicide application to large irrigation canals and lakes was laborious and time-consuming due to the presence of low submerged vegetation and high water velocity. Effective snail control at water contact sites required one to two applications per month per site. Follow-up cost-effectiveness studies (Werler, 1989) and the need for qualified personnel to carry out molluscicide application have limited its use during the last few years. Carefully designed studies in well-defined seasonal transmission areas still need to be conducted.

Graph 1: MALI OFFICE DU NIGER
Prevalence of schistosome infection before and 1 year after treatment

Analyzing the impact of mass chemotherapy with praziquantel on the prevalence and intensity of schistosome infection in all intervention areas, Brinkmann et al. (1988b) showed that the effect of a single treatment could last for more than two or three years. Chemotherapy has since played and will certainly continue to play a major role in schistosomiasis control in Mali.

Men watering vegetables (Plateau Dogon)

Children collecting water for vegetables (Plateau Dogon)

Chemotherapy has been the main control strategy in Office du Niger and Plateau Dogon. But managed by the central team based in the capital, this vertically oriented control program could cover only a limited number of villages.

Furthermore, the aggregate impact of mass chemotherapy should not be overlooked. Infection is a dynamic process; reinfection after treatment is the rule rather than the exception.

Consequently, it became crucial to define interventions capable of further reducing the frequency of retreatment needed to keep down the post-chemotherapy recovery rate of the parasite population. The horizontally oriented approach using primary health care services appeared to be the only alternative.

- A reasonable and acceptable national plan of action, defining strategies for different endemic areas based on a good understanding of disease distribution and dynamics.

- A well-trained regional and district health care staff willing to take more responsibility for planning and implementing schistosomiasis control as part of their routine work.

Dam wall and children playing in upstream water (Plateau Dogon)

Cost analysis done by Brinkmann et al. (1988c) showed that a strategy of up to four successive blanket mass treatments had a cost 1.8 times greater than annual per capita government spending on health. It is thus not surprising that the cost of schistosomiasis control by this means was beyond the country's capacity to sustain without outside funds (GTZ had withdrawn support).

Schistosomiasis control: Need for long-term commitment

The past four years have seen intensive moves towards a rationally based and truly national control program (Traoré, 1990). The prerequisite is long-term commitment, necessitating:

- Availability of praziquantel, either free of charge or at least affordably priced. Although in contradiction with the "Bamako Initiative," the price of the drug is making it inaccessible to poor rural household heads who might have to pay for the treatment of five to ten infected individuals each year.

● A reasonable managerial and implementation capability at intermediate and peripheral levels, to make diagnosis and treatment available to the people most in need.

● Last but not least, intersectoral collaboration between water development projects and health services.

Although well documented and in theory considered essential, in practice these considerations have never received the attention they deserve. There is an urgent need for better information, education and communication as well as an improved water supply and sanitation system. Although beyond the capacity of the department of health alone, these solutions are the key to schistosomiasis control in the long term.

Women and girls washing dishes in the main canal (Office du Niger)

● A clear and well-defined delivery mechanism as well as an operational and epidemiological monitoring system, in order to adapt strategies to any changes.

Men working in a rice field (Office du Niger)

A secondary canal and rice fields (Office du Niger)

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Typical clay buildings in a Dogon village (Mali)

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Women of the Plateau Dogon washing at a watering place (Mali)

Multi-Drug Therapy (MDT) for Leprosy Control

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Leprosy is a chronic granulomatous infection of humans which particularly affects the skin and superficial nerves. Its clinical and immunological manifestations are a spectrum with polar tuberculoid (paucibacillary) leprosy at one end and polar lepromatous (multibacillary) leprosy at the other. The disease generally follows an indolent course, interrupted by two types of reactional episodes: erythema nodosum leprosum (ENL) and reversal reaction, most often precipitated as complications of chemotherapy.

- diaminodiphenylsulfone), introduced in the 1940's by Cochrane and Muir in India, Lowe and Davey in Nigeria and Opromolla in Brazil. At present the principal anti-leprosy drugs are rifampicin, clofazimine and dapsone.

Principal drugs in use

Dapsone. This drug is cheap, safe, effective and eminently suitable for ambulatory treatment. Dapsone is bacteriostatic, though its exact mechanism of action is still unknown. A dose of 100 mg daily re-

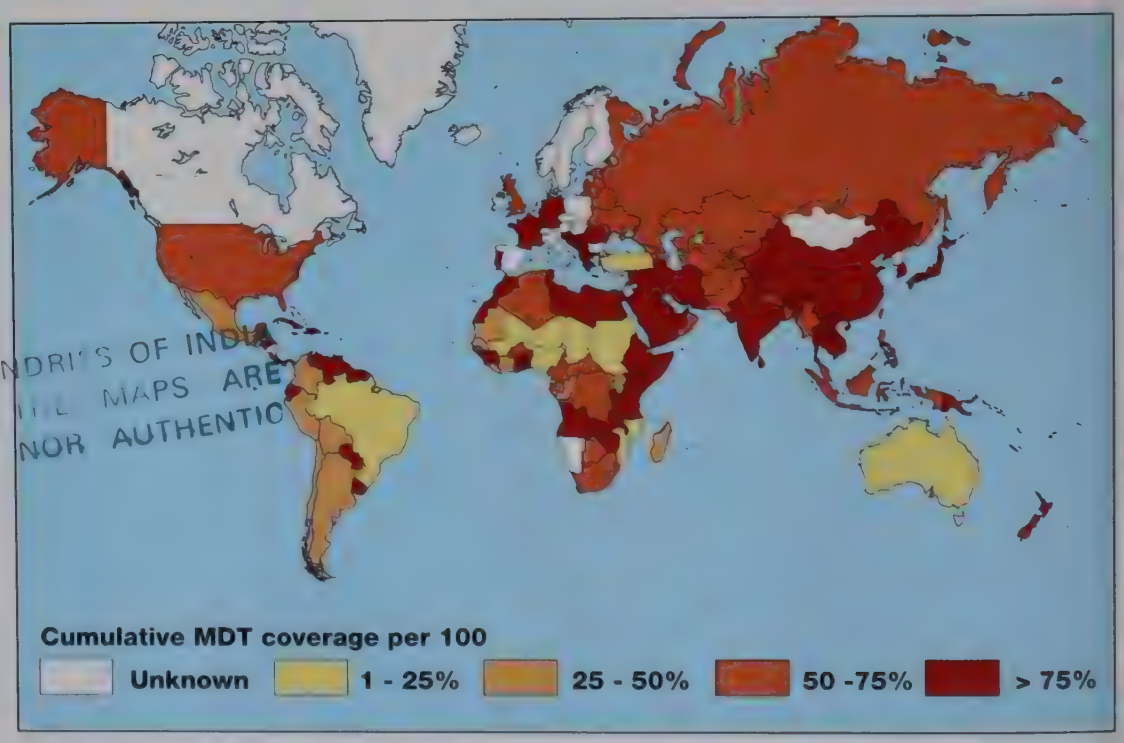

Fig. 1 Cumulative MDT coverage in the world as of February 1992

The treatment of leprosy was quite unsatisfactory until recent years. Multi-drug therapy (MDT) is the most significant advance made in its management. Until 1941 there was no really effective anti-leprosy drug. The first chemotherapeutic agent used against the disease was dapsone (DDS

sults in peak serum levels 500 times greater than its minimum inhibitory concentration (MIC). This large therapeutic margin is of great practical importance. At such a high concentration the drug is weakly bactericidal. It should be administered in a daily oral dose of 100 mg for adults

and 50 mg for children. Side effects are rare with the recommended doses. Clinical improvement is usually evident within three to six months of starting treatment. Failure to improve is a sign of possible dapsone resistance. Resistance during therapy (secondary resistance) is by and large limited to multibacillary leprosy. Treatment by dapsone alone leads to emergence of resistant strains of Mycobacterium leprae and microbial persistence.

Rifampicin. This is the most potent anti-leprosy drug in current use. It is rapidly absorbed and widely distributed in body tissues. Rifampicin's MIC against *M. leprae* is 0.3 mg/liter and a single dose of 600 mg will kill 99.9% of the bacilli within a few days, rendering the patient non-infective. The drug will not cure leprosy by itself as viable bacteria still persist in certain tissues even after two to five years of therapy. Moreover, several cases of rifampicin resistance have also been reported.[1]

The drug is best tolerated on an empty stomach. Treatment may take the form of either daily or monthly doses, the latter having the advantage of supervision, better compliance and considerable cost savings. A monthly dose of 1200 mg is considered ideal, but a 600 mg dose is a satisfactory alternative. The recommended dose is 600 mg and 300 mg monthly for adults and children, respectively.

The most common side effect is red discoloration of the urine. In rare cases rifampicin may cause hepatitis and thrombocytopenia. The drug is well tolerated but, if dosed intermittently, may give rise to a "flu"-like syndrome.

Clofazimine. This red dye is bacteriostatic against the lepra bacillus. Its overall anti-leprosy effect is the same as that of dapsone, with the added advantage of anti-inflammatory action. As a result the drug has been used effectively in treating the reactional states of the disease (Figs. 2 and 3). Clofazimine is best absorbed after meals and is unevenly distributed in the tissues, the highest concentrations reached in intestinal mucosa, lymph nodes and fatty tissues. For this reason it is not possible to calculate the drug's MIC. In general it is well tolerated and virtually non-toxic when given in doses not exceeding 100 mg daily.

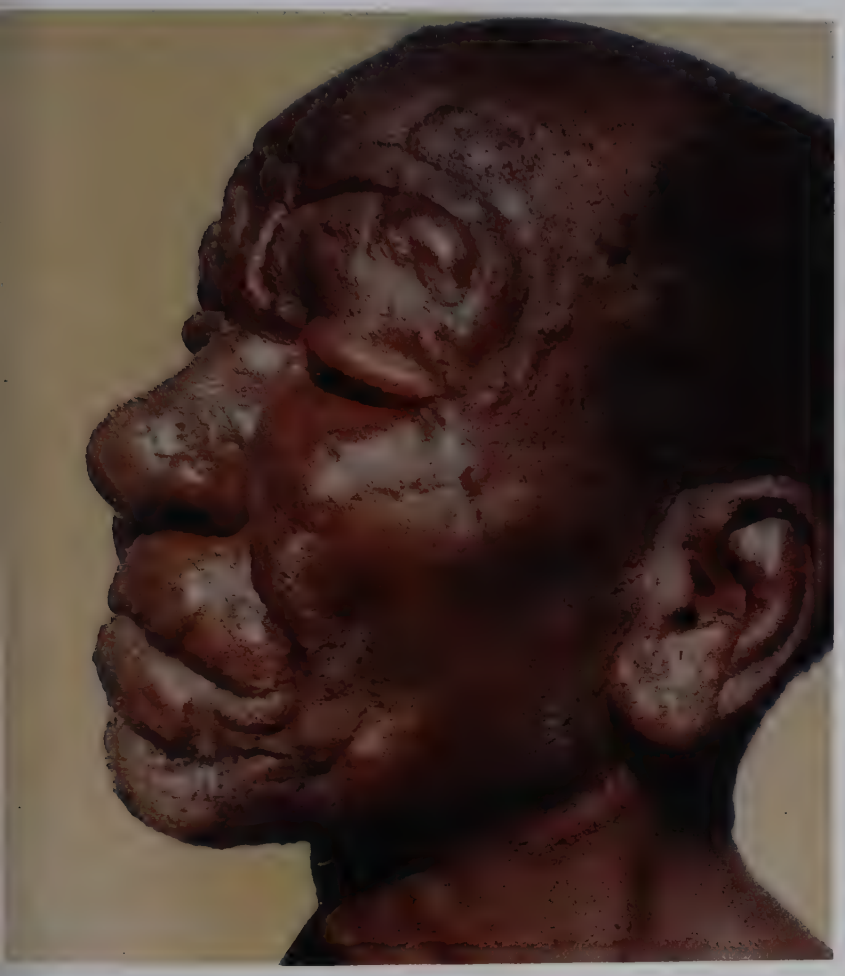

Fig. 2 Reversal reaction in a patient with borderline (BT) leprosy

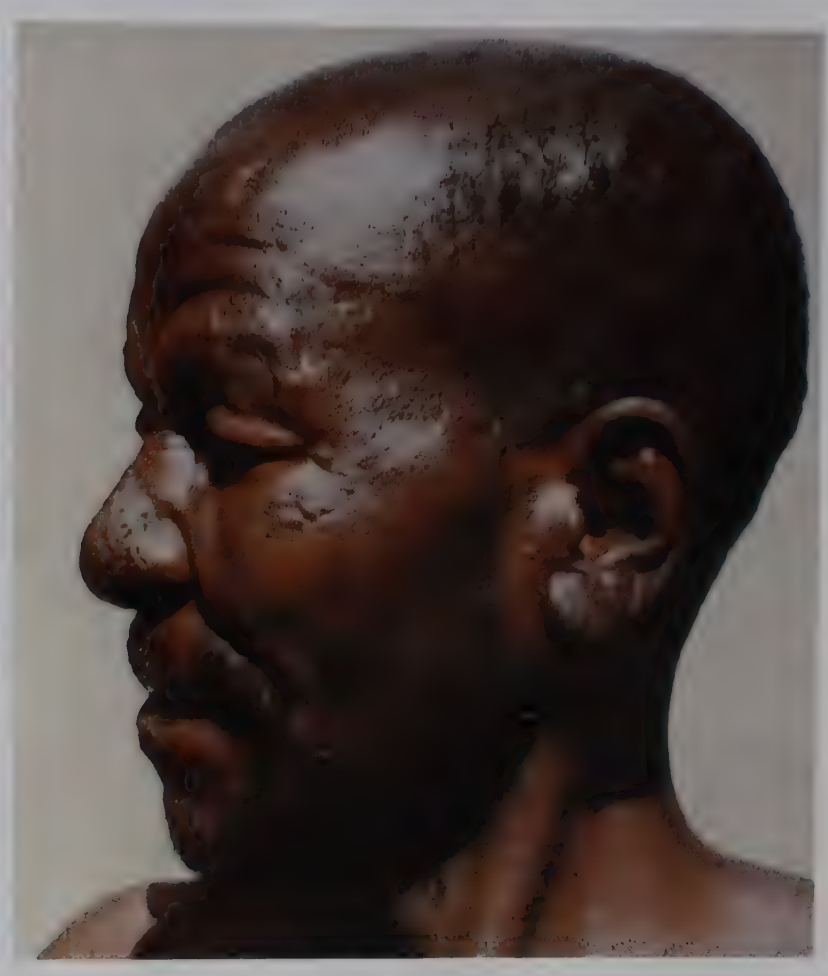

Fig. 3 The same patient (Fig. 2) after 2-month treatment with clofazimine

Resistance to clofazimine is very rare. The drug has been used on its own for many years to treat dapsone-resistant patients. The drawbacks are high cost, development of skin pigmentation and abdominal symptoms.

overcome with a combination of at least two potent drugs. Both drugs kill sensitive organisms or prevent their multiplication. At the same time each drug prevents the growth of organisms resistant to the other. The three drugs employed in MDT are dapsone, rifampicin and clofazimine. These must be used simultaneously, in full doses and for an adequate, uninterrupted period. The WHO recommendations assume that clofazimine is acceptable to children, so no child requires treatment with second-line drugs such as ethionamide.

daily, self-administered; clofazimine 300 mg once per month, supervised, and 50 mg daily, self-administered. Treatment should last for at least two years and continue, if possible, up until smear negativity.

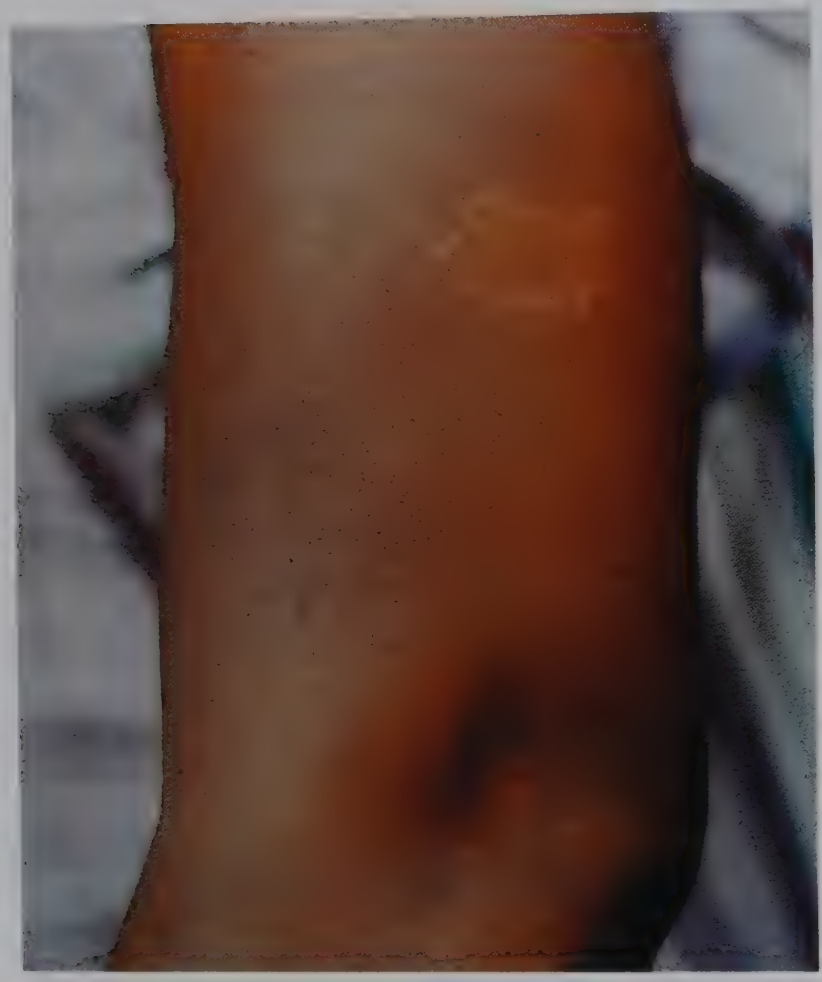

Fig. 4 Lesion of paucibacillary on arms pre-MDT

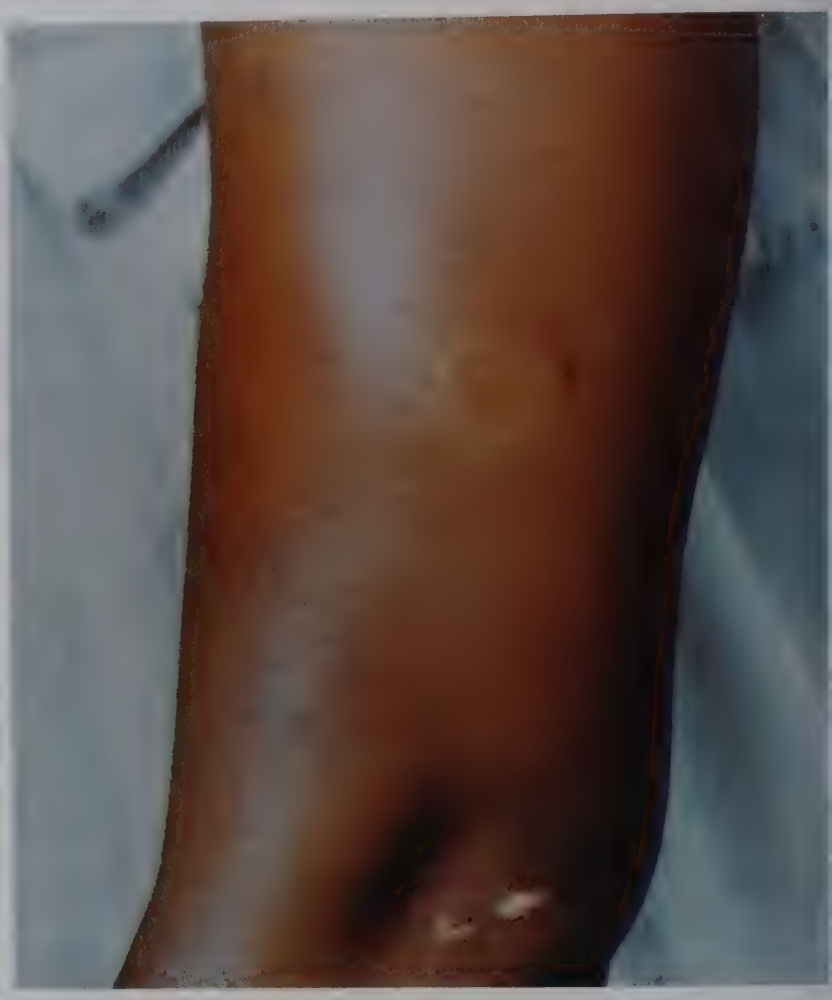

Fig. 5 The same lesion (Fig. 4) after 6-week multi-drug therapy

Multi-drug therapy (MDT)

At one time the chemotherapy of leprosy patients was confined to dapsone. The first report of dapsone resistance appeared in 1964.[2] Since then there has been a steady increase in secondary dapsone resistance worldwide.

In 1982, following the deliberations of a study group[3], the World Health Organization (WHO) drew up specific recommendations for treating leprosy on an MDT regimen. The problem of drug resistance is

The combined drug therapy is designed for all categories of multibacillary patients: the newly diagnosed, those responding satisfactorily to earlier dapsone therapy and those who have relapsed after dapsone treatment. The treatment schedule consists of: rifampicin 600 mg once per month, supervised; dapsone 100 mg

Paucibacillary patients require rifampicin and dapsone, administered in the above doses and manner over a period of six months. The treatment is meant for all freshly diagnosed cases, patients treated with dapsone who have relapsed and others who are currently on dapsone monotherapy but have not yet completed two years of therapy.

Several chemotherapeutic trials have confirmed the effectiveness of MDT. Multibacillary patients are rendered non-infective within two weeks of treatment, skin lesions im-

prove (Figs. 4, 5, 6, and 7) and there is complete clinical, bacteriologic and histologic regression of the lesions. The frequency and severity of ENL reactions are significantly reduced.[4]

disease prevalence, no parallel decline occurred in disease incidence in spite of well-organized and effectively implemented dapsone-based programs. There is now sufficient evidence[5] from field studies undertaken by THELEP* at Chengalput, Karigiri and Polambakkam in India and Bamako in Mali to establish that

cases by 1993, the cumulative coverage being 80%.[7] However, a recent WHO report[6] draws attention to considerable regional variation in world coverage with MDT. While the countries of the Southeast Asian and Western Pacific regions have achieved satisfactory results, the case is not the same elsewhere (Table 2).

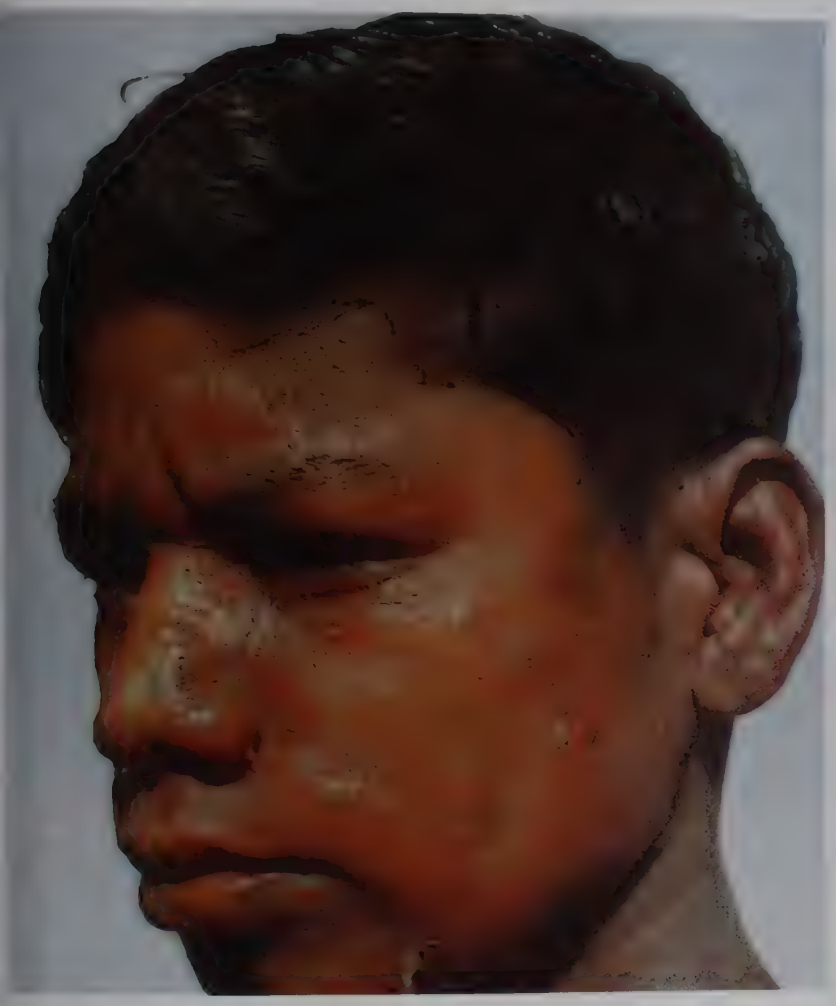

Fig. 6 Lesion of multibacillary (BB/BL) leprosyon the face pre-MDT

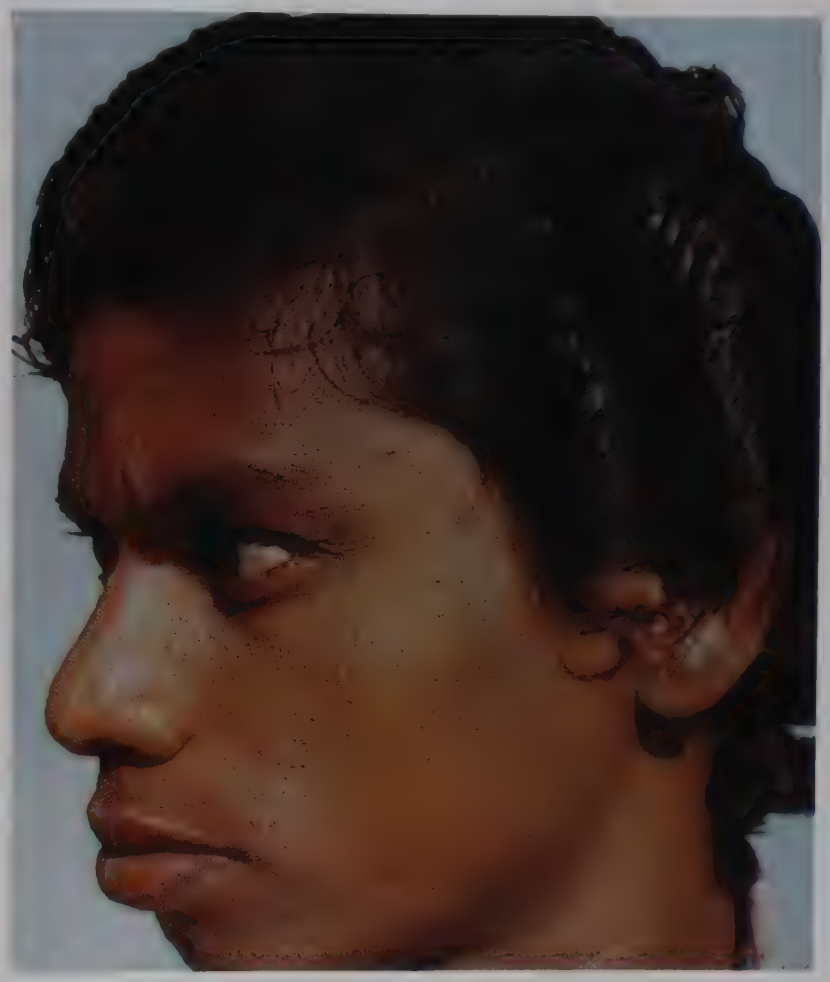

Fig. 7 The same lesion (Fig. 6) after 12-month multi-drug therapy

Multi-drug therapy for leprosy control

In recent years the limitations of the leprosy control strategy using dapsone monotherapy have become increasingly obvious. While certain regions such as Thailand, central Myanmar, Burkina Faso and southern India showed substantial decline in WHO-recommended regimens are capable of preventing and overcoming dapsone resistance.

Almost all leprosy-endemic countries in the world have adopted MDT for leprosy control. There has been remarkable progress in the worldwide coverage of leprosy patients by MDT (Fig. 1). As Table 1 shows, progress was slow to begin with, covering only 8.8% of registered cases in 1986. By 1991, however, coverage had rapidly spread to 67%. Worldwide MDT coverage had reached 46% of total registered

Control programs in Africa have advanced particularly slowly. Compared with 66.2% MDT coverage achieved for Southeast Asia in 1990, the overall rate in the African region was only 18.4%.

The very wide acceptance of MDT is attributable to several advantages it offers over dapsone monotherapy. MDT prevents drug resistance, combats pre-existing dapsone resistance infection and eliminates the need for time-consuming determination of dapsone sensitivity before starting therapy.

* Chemotherapy of Leprosy Scientific Working Group under the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases

MDT drastically reduces the period of treatment and cures rather than arrests the disease. The patient is quickly rendered non-infective, minimizing the chances of disease transmission. More importantly, MDT cuts down the long-term cost of control programs.

worldwide has declined for the first time (Table 1). From a total of 5.4 million registered cases in 1985, the number dropped to 3.2 million in 1991 - a decline of 40% over a six-year period. This was mainly made possible by MDT implementation. In addition, decreases in new case detection, prevalence and disability annual case detection and deformity rates and a decline in childhood leprosy (Table 3). Operationally, MDT improved self-reporting by patients and prompted excellent treatment compliance.

Table 1: Worldwide progress of multidrug therapy implementation

Year	1985	1986	1987	1988	1989	1990	1991
Registered cases (in thous.)	5,368	5,341	5,078	4,908	3,866	3,737	3,205
No. of cases on MDT	78,757	468,222	1,318,964	1,604,927	1,751,903	2,080,998	2,161,045
% of total cases	1.47	8.77	25.97	32.70	45.32	55.69	67.42
No. of cases completing MDT (cumulative total)	9,425	93,216	515,144	627,919	853,706	1,204,825	1,411,468

Table 2: Level of coverage for MDT in leprosy endemic countries –1991

SNO	MDT Coverage %	Countries in WHO regions with MDT						
		Africa	Americas	Europe	Eastern Mediterranean	South-east Asia	Western Pacific	Total
1	>76	12	11	0	3	3	12	41
2	51–75	8	2	0	1	4	5	20
3	26–50	4	6	0	0	1	1	12
4	11–25	6	2	0	2	1	0	11
5	1–10	5	0	0	1	0	0	6
6	No information	0	0	0	1	0	0	1
	Total	35	21	0	8	9	18	91

Table 3: Epidemiological impact of multidrug therapy (MDT) in 12 districts in India

SNO	Indicator	At commencement of MDT	March 1989	Reduction (%)
1	Prevalence rate per 1000 population	9.8	3.4	65.3
2	New case-detection rate per 1000 population	3.1	1.8	42.0
3	Multibacillary ratio (%)	24.7	21.3	13.8
4	Child rate (%)	18.8	16.3	13.3
5	Deformity rate (%)	7.6	2.7	64.5
6	Number of villages with leprosy patients	15,487	11,251	27.4

Issues in leprosy elimination with MDT

WHO has set the goal of eliminating leprosy by the year 2000. Since the biological balance between man and leprosy is almost equal and infected individuals are the only source of further human infection (with the exception of wild armadillos in the United States), it is logical to assume that universal coverage with MDT will eradicate leprosy. However, several variables exist which complicate the situation.

The lowest prevalence rate necessary before disease transmission ceases is not known. It has been arbitrarily assumed that at a prevalence of 1 case per 10,000 inhabitants, the disease load in the community would be so low as to make transmission potentially negligible, with the result that leprosy would die out by itself.

Because of prolonged duration of the disease, the prevalence rate of leprosy under natural conditions is 10 to 15 times greater than its annual incidence. MDT has dramatically inhibited prevalence and considerably shortened the treatment period, reducing the reservoir of infection. Still, it remains to be seen whether MDT will make the disease incidence fall as quickly - and that will determine how long it takes to eliminate leprosy.

Furthermore, there are several problems in providing universal MDT coverage to leprosy patients. The progress of MDT is impeded by poorly developed infrastructure, lack of trained personnel, competitive claim of other diseases like malaria, tuberculosis and AIDS to limited national finances, lack of laboratory fa-

Though it is far too early to assess the global impact of MDT on leprosy status, certain trends are nonetheless discernible. In spite of the considerable increase in newly detected cases during MDT implementation, the total number of registered patients

rates following MDT have been reported in several countries including India,[8] French Polynesia[9] and Indonesia.[10] The Indian study[8] of twelve endemic districts under MDT cover for over three years showed a marked reduction in prevalence,

cilities, paucity of referral services to treat complications and limited availability of drugs.

Another issue related to MDT strategy is the case of the disabled. MDT provides only for primary prevention of deformities through early treatment and cure. Even after disease transmission is arrested, the need for rehabilitation of the disabled will continue.

Lastly, while MDT has raised hopes of leprosy elimination, it still remains a strategy for arresting disease in established cases. It is possible that there will still be a need for a more fundamental approach of primary prevention by protecting individuals at risk.

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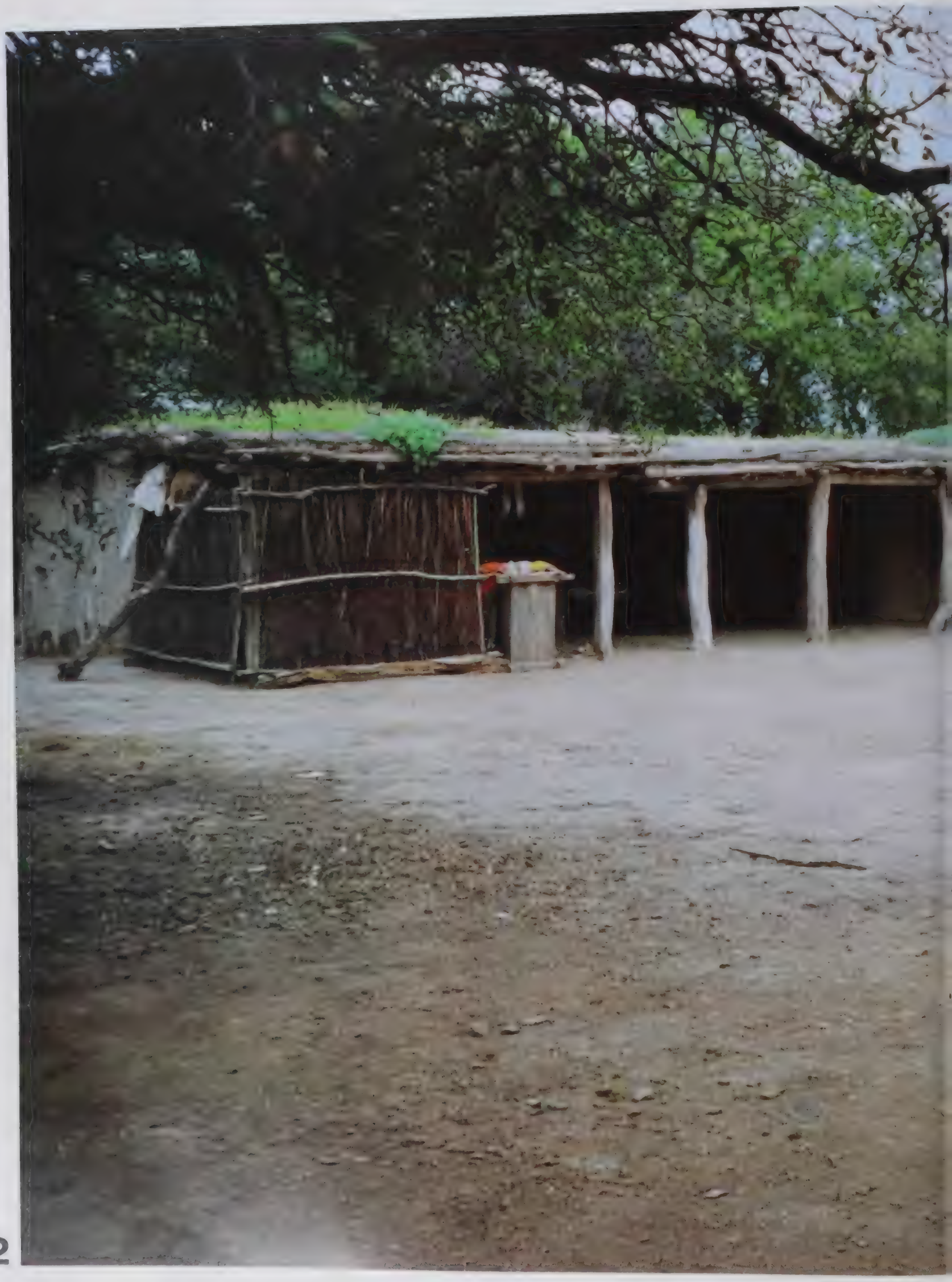
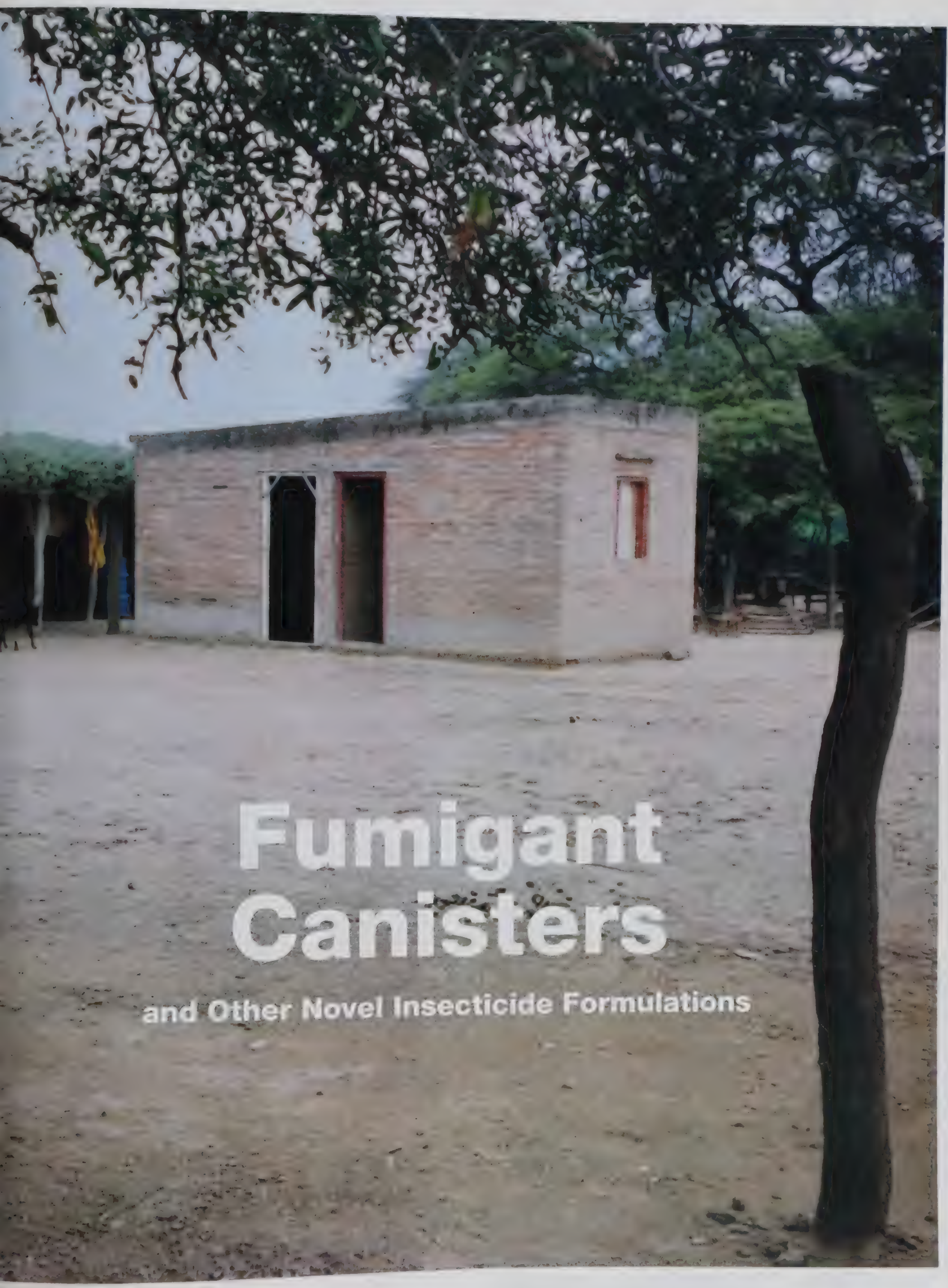



Fumigant
Canisters
and Other Novel Insecticide Formulations

Dr. Eduardo Zerba
Director, Research Centre of Plagues and Insecticides (CIPEIN) of Argentina
Argentina

the major public health problems faced by developing countries. It is obvious that the operations directed to control insect vectors represent an essential preventive measure. At the beginning of the century, emphasis was placed on the need to organize and implement control programs, reduce endemic diseases and prevent or control epidemics. Several countries in the Third World implemented centralized control programs based on government-sponsored professional sprayer teams.

Control of insect vectors: Centralized campaigns or community participation?

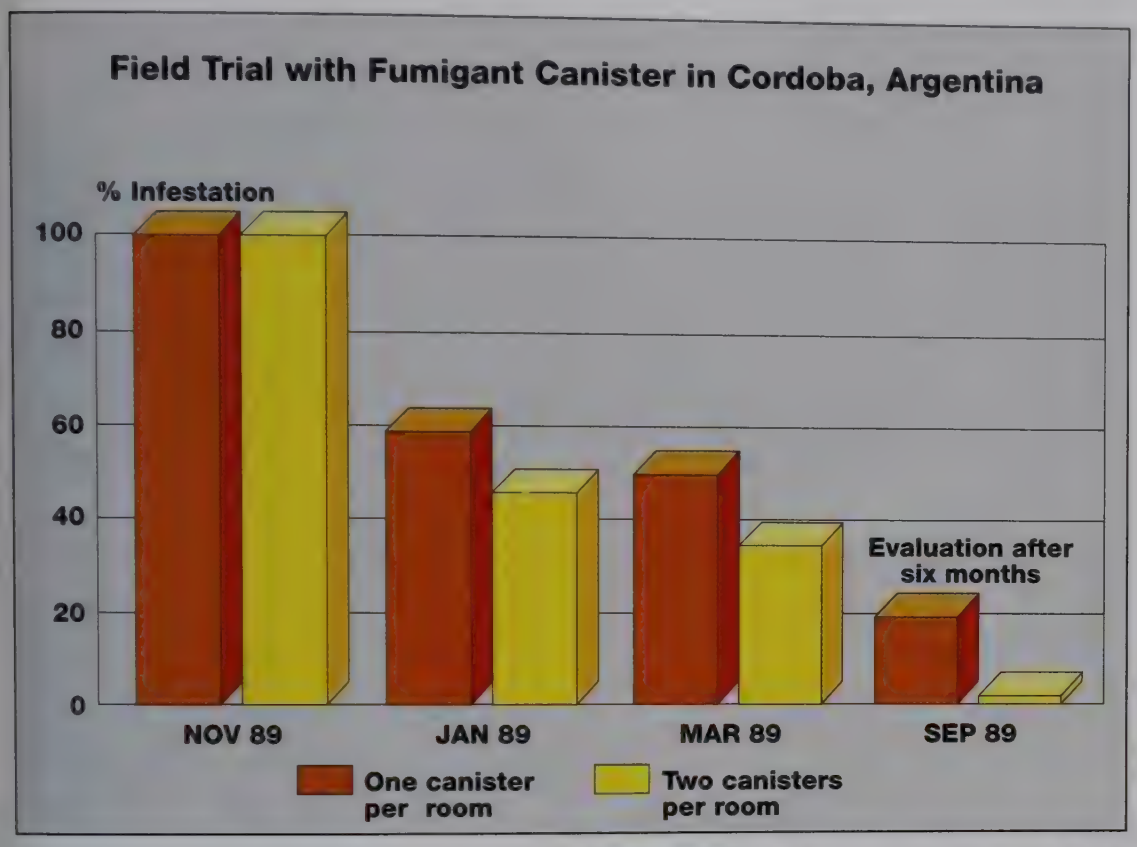
In 1978 the Declaration of Alma-Ata defined a series of points necessary to achieve a goal by the year 2000: health care available to everyone (WHO, 1979). To reach the objective of health for all, it will be necessary to prevent and control tropical diseases whose transmission is mediated by insect vectors. Vector-borne diseases have a very complex pathogenesis and constitute one of

Residual treatment of the inside of dwellings with DDT at 1-2 g/m^2 was one antivectorial campaign directed against *Anopheles* mosquitos, vectors of malaria. Spraying indoor areas and adjacent structures with HCH at 0.5 g of the isomer/m^2 to control triatomine bugs was a typical Latin American technique used in national programs to combat Chagas' disease.

This type of centralized campaign has not been sufficiently effective because of the cumbersome and costly techniques used. In some cases, control activities were imposed on the community by coercive measures. In addition, intensive use of old chlorinated hydrocarbon insecticides has not proven to be an ecologically sound solution. Another major obstacle facing national programs against vector-borne diseases is the development of vector resistance to different active ingredients.

Pages 62 and 63:
Typical rural dwelling of Argentina infested with Chagas' disease vectors

Things could change dramatically with the transfer of vector control operations to the village level. But community participation needs new tools as part of a novel practical strategy to reduce vectorial transmission of tropical diseases. For successful development of a decentralized strategy, the new tools should be effective under local epidemiological situations and compatible with the cultural context of the community at risk. Moreover, if the new tools proposed include insecticide formulations, these should be safe enough for use by non-experts.



Typical rural dwelling of Argentina infested with Chagas' disease vectors

The fumigant canister as new control tool

One example of a safe formulation for use by non-professionals is the fumigant canister, developed in Argentina for indoor use against Chagas' disease vectors. The high insecticidal activity of the fumigant canister against triatomine bugs can be attributed to its insecticide formulation, based on a new type of synergism. Laboratory studies have demonstrated that triatomine bugs consume more oxygen after treatments with sublethal doses of pyrethroids or lindane vapors. Thus consecutive treatments with vapors of an activator of insect respiration and a fumigant insecticide such as dichlorvos produce higher insect mortality than observed with individual treatments. This particular type of synergism was useful in developing the insecticidal fumigant canister, which consists of a disposable canister containing a solid fumigant mixture and a plastic vial. Simply lighting a fuse on the top begins the foolproof operation. The first step involves combustion (without a flame) of the solid mixture, producing a rapid release of combustion gases containing a pyrethroid activator of insect respiration. This active principle is incorporated into the mixture using adequate protective measures to avoid thermal or chemical decomposition during combustion. The heat produced during combustion (step 1) causes fusion of dichlorvos and another pyrethroid in the vial, followed by release of vapors and fumes (step 2) (Zerba et al., 1988).

Although fumigant canisters are especially suitable for community participation, their success in centralized operations has been demonstrated in different field trials. The National Chagas Service of the Argentine Ministry of Health performed a field trial in Las Tapias and San Javier, two villages located in the province of Cordoba, Argentina. The trial consisted of three indoor treatments with two different doses, with either one or two fumigant canisters per room. The treatments took

place in November 1988 and January and March 1989. An evaluation of house infestation with nymphs and adults of *Triatoma infestans* was done in September 1989. The entomological evaluation after the last fumigation cycle showed that, over a period of six months, dwelling infestation had fallen from 100% to 16% with one canister per room and from 100% to 0% with two canisters per room (J. Cichero, unpublished results, 1989).

Another successful use of the fumigant canister to control Chagas' disease vectors was through an entomological surveillance approach based on a primary health care system. The approach was implemented in a rural area of Santiago del Estero, northern Argentina. The surveillance design included the use of triatomine detection boxes for entomological diagnosis and fumigant canisters for decentralized control operations. Four years after the beginning of the surveillance program, seropositivity had dropped from 5.5% to 0% in babies under one and from 12.4% to 0% in children under four. The cost of the entire intervention including canisters, detection boxes, personnel, etc. was estimated at US$4.7 per house per year, five times lower than the cost of the vertical governmental campaigns (TDR News, 1990, and Elsa Segura, personal communication, 1990).

Pyrethroid impregnation of fabrics under field conditions

Fumigant canister treatment in a rural dwelling

Application of the insecticide to household goods in governmental campaigns against insect vectors

In short, fumigant canisters represent a new control tool against insect vectors, useful not only for decentralized operations involving community participation but for governmental campaigns as well (Zerba, 1989). The most recent national antivector program in Argentina was also based on fumigant canister use.

Within the framework of this campaign, which ran from 1991 through 1993, canisters were placed in 380,000 houses in the endemic area (TDR News, 1991).

Professional sprayers working to control the insect vectors of tropical diseases

Impregnated bednets and fabrics

Bednets and window screening have long been considered a useful barrier against mosquitos and other disease vectors. It is obvious that treating mosquito nets with a repellent or lethal insecticide will enhance their protective effect. The first evaluation of cotton mosquito nets treated with organophosphorus insecticides was in Burkina Faso (Brun & Sales, 1976). The approach became more promising with the advent of safe and quick-acting synthetic pyrethroids.

Photostable pyrethroids such as deltamethrin and permethrin were highly successful in early field trials of impregnated nets. Possible effects on mosquitos after contact with impregnated nets include deterrence (i.e. not entering houses), inhibition of feeding, exito-repellency and adult insect mortality.

Several village-scale trials using pyrethroid-treated nets were performed in the 1980's in some areas of Asia and Africa. In spite of operational problems discovered during the field trials, the results were considered sufficiently promising for large-scale introduction of impreg-

nated nets in different countries, for example in China, Vietnam and Papua New Guinea (Rozendaal, 1989).

In countries where this control strategy has been adopted, training and supervision is usually provided by local health staff trained in net impregnation methods. The role of the local health workers is to manage the procurement of insecticides and netting for the community to carry out initial and subsequent impregnation. Specialists recognize some knowledge gaps about the use of pyrethroid-impregnated nets as regards community participation in the management of the control technique. But in spite of the doubts and criticisms, the use of insecticide-treated nets as a form of malaria prevention and control has been accepted as a successful strategy. In China over five million people are currently protected with treated nets and a recent study conducted in Gambia demonstrated a substantial reduction in rates of malaria-dependent child morbidity through use of impregnated bednets (TDR News, 1991).

Another innovative approach initiated in Argentina to control Chagas' disease vectors is based on pyrethroid-impregnated fabrics. In an ongoing field trial in the province of Santiago del Estero, supported by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, these fabrics are placed under roofs, between furniture and walls, and under mattresses in infested dwellings. The present performance results of the pyrethroid-impregnated fabrics show high insecticidal activity, very long residual activity, lack of undesirable side effects, and excellent acceptability by the community involved, which is encouraged to participate in control activities (E. Wood & E. Zerba, unpublished results, 1992).

The insecticide formulations described above represent part of an effort to innovate vector control strategies. Reaching the objective of "health for all by the year 2000" will require new tools for vector control and novel strategies which should be integrated into the primary health care system, with active community participation

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Chagas' Disease.

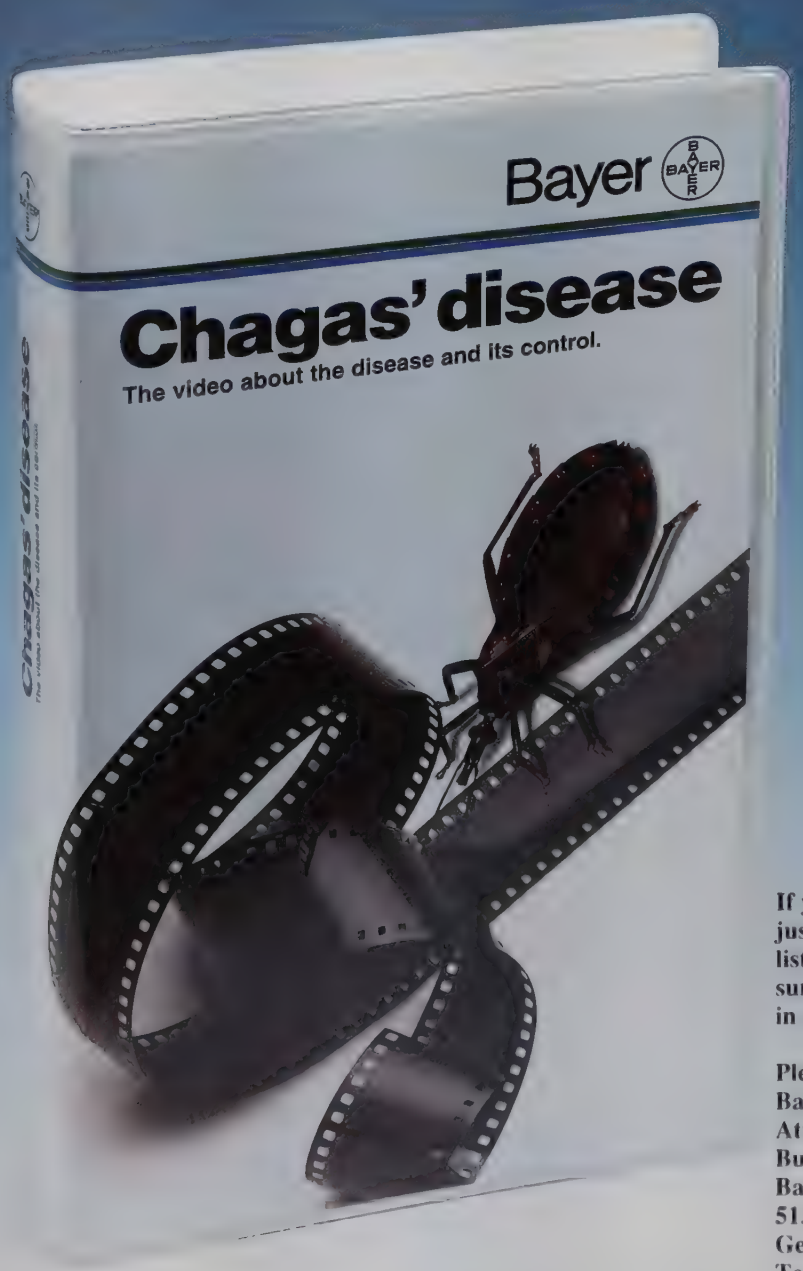
The video about the disease and its control.

Chagas' disease occurs only in the Latin American region where, according to WHO, the bugs that transmit it, and the trypanosomes that cause it, pose a threat to some 90 million people. Between 16 and 18 million people are already infected.

The film shows the symptoms of the disease which is generally transmitted in childhood. It also points out the unmistakable but unfortunately rare signs of infection.

The so called "Sissing" bugs that transmit the disease are found most commonly in the huts in which poor people live but also in other hiding places.

The best prospects of controlling the scourge of Chagas' disease locally are offered by eliminating the disease vectors. Bayer has the necessary effective insecticides and also provides technical and scientific cooperation in the planning and implementation of vector control programs.



If you would like a copy of this video, just send your request to the address listed below (IMPORTANT: Make sure to ask for the video format used in your country).

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Bayer: Expertise in tendering

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Coordinated teamwork for maximum effectiveness

Effective gains against epidemics and disease - no matter which part of the world they beset - call for all concerned to put their specific expertise to work seeking solutions to what are often quite complex problems.

Tenders: First step towards solutions

A vital ingredient in problem management is acquisition of the necessary products, equipment, materials, etc., generally done through tenders. For animal health and vector control, projects are initiated by federal, state, municipal or community agencies and financed at national or international level. Because of the diverse nature of the problems involved and the variety of potential contact partners, good coordination and cooperation are of the utmost importance.

Social responsibility

Animal health and vector control ultimately affect human health - one reason why Bayer is committed to tackling these daunting challenges. As a major market player with operations spanning the globe, we see it as our obligation to contribute our resources and worldwide expertise to the active quest for solutions. Joining efforts with partners and promoting cooperative ventures, we have seen our team-player approach to problem-solving confirmed many times over in practice with both partners and customers.

New structures for effective project management

The growing complexity of managing global tenders effectively closed the chapter on the purely commercially-minded approaches of the past. Faced with the increasing demands of project management, our Animal Health Division made the proactive decision to develop a future-oriented strategy, following in the footsteps of the Health Division. Structural and logistical changes were made which now significantly boost our ability to take on the tasks at hand.

Animal Health & Vector Control Consulting Group

Since January 1995 a new unit has been handling all aspects of tenders at Bayer: the Animal Health & Vector Control Consulting Group. The formation of this Group heralds our new concept of internal cooperation and task-sharing between centralized and local participants.

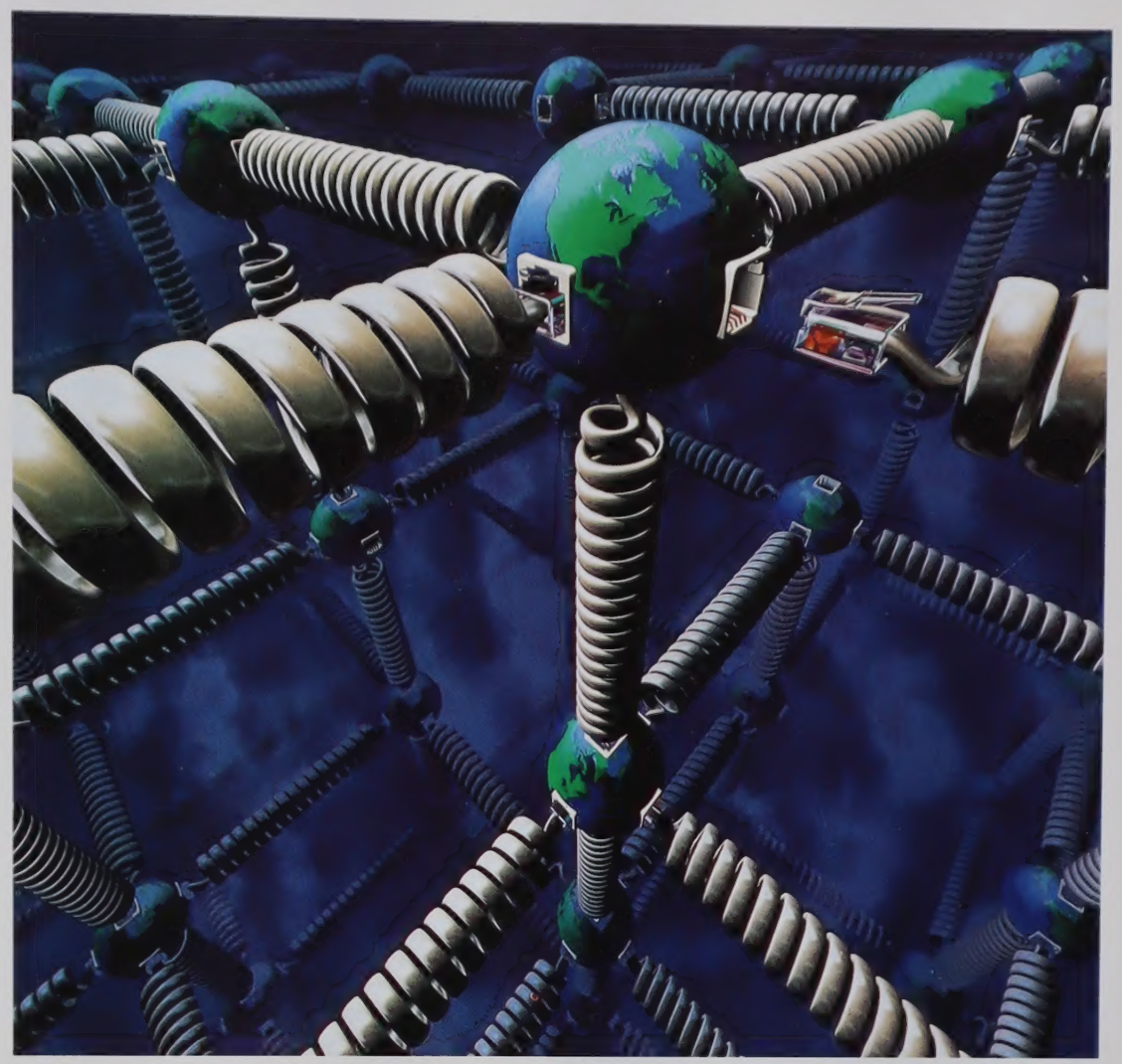
ANIMAL HEALTH VECTOR CONTROL
CONSULTING-GROUP

Heightened performance on site

The existence of the centralized Consulting Group is a clear boost to the performance power of the local organizations (participating companies, agents, etc.). The Group concentrates its efforts on synchronizing the specific responsibilities and duties of the local/regional offices with those of Bayer headquarters. The upshot is optimization of Bayer's overall performance - a benefit for all concerned.

Coordination and information

The experienced members of the new Animal Health & Vector Control Consulting Group see their principal role as liaison and bridge. The most important fields of activity center around supporting interfaces between local agencies and institutions of international scope, managing and promoting projects in the early planning stages, coordinating the logistics of product supply with customers' requirements during the tendering process itself, etc.



An optimal organization is the main condition for an optimal presentation

The Group is designed as a reliable resource and partner for the institutions, public authorities, engineers and all others involved, ensuring multilateral communication that serves the ends of the individual projects.

An additional sphere of activity is development of individual project-specific strategies to achieve just the right balance between technical concerns and financial interests.

Solutions call for all-out commitment

Our philosophy is that solutions go beyond offering products - a viewpoint which sets Bayer apart from conventional suppliers. Even more valuable is the ability to provide the agencies and institutions concerned with full service packages. Facets of such all-around service include pre-liminary processing of information, training courses (notably the "Train the Trainer" programs), state-of-the-art application methodology, assistance with financial models, post-sales service, resistance management, integrated solutions, etc.

Quality teamwork ultimately makes for quality performance

The Animal Health & Vector Control Consulting Group is convinced that compiling all types of topical data and building bridges between contacts at various levels is a promising strategy for achieving better results more quickly. The Group

currently works together with WHO, FAO, the World Bank and other UN organizations and maintains close ties to relevant EU entities and public authorities in the individual member states (GTZ, DANIDA, etc.). Intensive links are also maintained and cultivated to leading scientific institutions which count as opinion leaders.

Thanks to its contacts and sphere of activity, the Consulting Group based at Bayer headquarters serves as a valuable interface between the individual organizations and, most of all, between headquarters and our own units at local level. The Group fills the function of liaison office and troubleshooter when it comes to coordination glitches or when existing specialist or practical knowledge needs tapping and disseminating.

Key role of local units

At the same time, however, optimum management of tenders depends on the groundwork laid at grassroots level by grassroots resources. The only guarantee of success is interplay between local project management and international coordination which is characterized by close collaboration and trust.

Wide-ranging problems demand wide-ranging product palette

The diverse nature of the existing problems calls for a broad spectrum of products. With our current range on offer, specific new developments, targeted licensing projects and cooperation with other companies, Bayer AG feels confident that the right foundation for this is firmly in place.

Perspectives for the future

The official launch of the Animal Health & Vector Consulting Group as a link in the international chain of communication, plus the close teamwork between the Bayer Group and its local units, forms a solid, future-oriented basis for finding solutions to the problems of tomorrow.

Information

For more detailed information, please contact us at:

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or send a fax to
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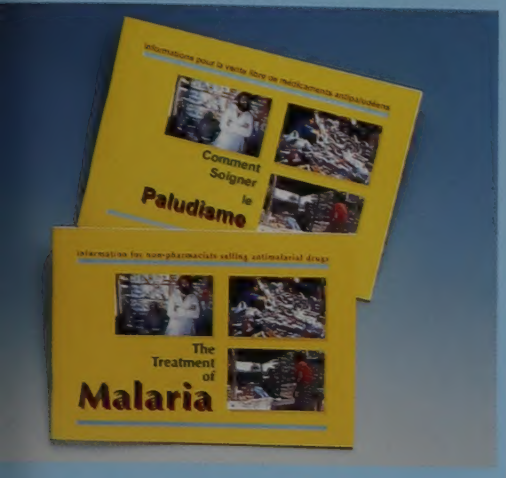
NEWS

WHO BOOKLET NOW AVAILABLE



The booklet "The Treatment of Malaria" is now available in English and French.

Please contact the Division of Control of Tropical Diseases Training Unit within the

World Health Organization
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Training Unit
20, Avenue Appia
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Switzerland
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WHO VIDEO NOW AVAILABLE

The video "Dengue – A Sinister Dawning" is now available for sale. This video, developed in collaboration with the MANTEAU project, is available in English, French and Spanish.

Please contact the Distribution and Sales Unit at the following address:

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